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STATUS THYMICO-LYMPHATICUS

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PART I: HISTORICAL BACKGROUND AND CONSIDERATION OF NORMAL THYMIC WEIGHT

SINCE the time of Restelli (1845),[1] reviews of the literature with case collections and the reports of individual investigation of the thymus gland have appeared in the literature. Unlike the development of knowledge regarding most organs and problems, there has been no definite trend of thought regarding the thymus gland, nor have any salient and directional discoveries been made to indicate the function of the thymus, or for that matter, the constitution of the gland. For instance, embryologically it is common knowledge that the thymus, together with the parathyroids, arise from the third, and sometimes the fourth, branchial cleft, the thymus from the ventral, and the parathyroids from the dorsal diverticulum. Here, definite knowledge of the thymus gland ends and in the literature one finds from this point a gradual progression of confusing details regarding the anatomy and function of the organ. It has been suggested that inasmuch as the thymus and parathyroids are intimately associated in their development, that they may possibly share some function in common, and it is not an unusual thing to find parathyroids frequently embedded in the thymus gland or fragments of thymic tissue surrounding parathyroids in their normal position (Fig. 1). The anlage descends in the neck, the gland locating finally in the lower part of the neck or upper part of the thorax. But it does occasionally diverge from this course and is seen surrounding the epithelium of branchial pouches or clefts and occasionally thyroglossal cysts and ducts. Inasmuch as it is epithelial in origin, one might presume that it is epithelial in structure in the fully developed stage, and Pappenheimer[2] regards it as an epithelial organ both in derivation and in adult or fully developed structure. Cowdry,[3] on the other hand, states that "the thymus undergoes lymphoid transformation as vestigial structures, such as the vermiform appendix, have a tendency to do." It should be indicated, however, that this is not a parallelism, inasmuch as the lymphoid elements in the appendix are unassociated with the epithelium, but exist as true follicles, producing lymphocytes, the follicles being part, actually, in an anatomical sense, of the abdominal lymphatic chain, while in the thymus gland the cortex or lymphoid part of the gland is, as far as can be determined, a lymphoid

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structure in appearance only. Further confusion exists in considering the medulla where definite epithelial cell structures are seen producing concentric keratin or Hassall's bodies. These are cytologically epithelial in type but considered by some to be reticular cells, capable of phagocytosis. As concerns both cortex and medulla, no secretory function has even been established. On the other hand, many theories have been advanced regarding function of the thymus and while none of them have been proved, there is a reasonable probability that some of this theory is more than supposition. In 1858, Friedleben,[4] after protracted studies, concluded that the thymus was not indispensable but that it had an important bearing on blood formation, nutrition, and growth. Basch[5] in 1903, emphasized its importance in the young and indicated that thymectomy in young subjects would result in a form of osteomalacia or rickets, believing that the thymus was concerned in some way with the growth and calcification of bones. This relation to calcium metabolism was also suggested by Hewer (1916)[6] and Nitschke (1928).[7] Beginning in 1906 and continuing for over two decades, Hammar[8] carried on careful progressive studies

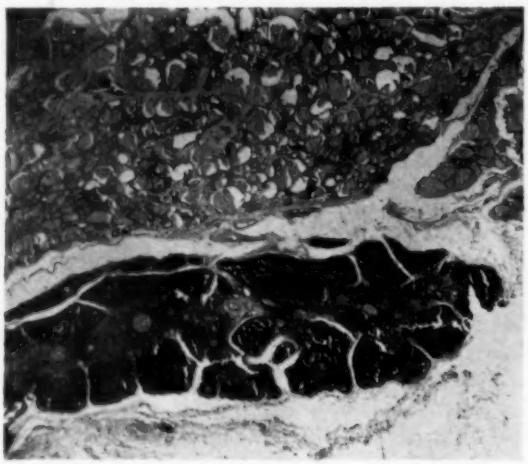

Fig. 1.—Thymus, both cortex and medulla, surrounding parathyroid tissue at lower pole of the thyroid gland.

on the growth and development of the thymus gland with its involutions in adults, establishing our present knowledge of the behavior of the thymus during the development and aging of human subjects. During that same time, from 1910 to 1914, Klose and Vogt,[9] working on the thymus, observed that in the young, thymectomy was followed by a latent period, then adiposity, and finally a period of cachexia with nutritional disturbances, spontaneous fractures of the long bones and, occasionally, death of the subject. Park and McClure (1919)[10] summarized the entire subject, recorded their own experiments, and drew four simple conclusions. They thought that the thymus gland was not essential to life in the dog; that its extirpation produced no detectable alteration in hair, teeth, contour of the body, muscular development, strength, activity, or intelligence of the experimental animal; that extirpation of the thymus probably did not influence growth or development, although it possibly caused retardation in development and closure of the epiphyses; and that extirpation probably caused no alteration in the organs of internal secretion. Young and Turnbull,[11] in 1931, were sent into this confusing maze of theories

by the Status Lymphaticus Committee working under the auspices of the National Research Council of Great Britain, but they emerged unfortunately with little more theory of acceptable character than was proposed before their work and established no new facts concerning the function or development of the gland. In fact, by their stated position, doubting the presence of such a syndrome as status thymico-lymphaticus, they probably did more to confuse the issue than they did to clarify it. There has not, as a matter of fact, even been any unanimity of opinion regarding the weights of the thymus gland at various ages. Hammar[8] found the thymus weight at birth to be 12 grams; at 5 years, 25 grams; at 10 years, 25 grams; at puberty, 37.5 grams; and at 20 years, 25 grams. Young and Turnbull,[11] however, give the average weight of the thymus at birth as 21.3 grams, and find a gradual increase until puberty to 34 grams, after which the weight gradually diminishes so that at midlife it is in the neighborhood of 15 grams. The only common opinion apparently remains to be that the thymus is relatively and absolutely largest during the period of greatest growth and that the gland begins involution at puberty, thereafter diminishing in size until death of the individual. By weighing the thymus gland of 500 children from 1 to 10 years of age, autopsied at the San Francisco Corner's Office in 6 years, we have been unable to corroborate or disprove these figures or those of Michael[12] and others, finding instead that the gland weight varies so greatly, that the best one could hope to establish is an average weight, the normal weight actually fluctuating widely with other factors.

These factors specifically are the constitutional heritage, the state of nutrition and type of diet, infectious diseases, and the influence of other endocrine glands. There is also a marked difference in thymic weight, depending on the locality in which the babies have lived preceding their death, the gland being somewhat heavier in cooler climates and lighter under conditions where the residence has been in locations of tropical or subtropical temperature. The largest average weight of the combined two lobes and capsule of the gland has been seen in very well-nourishd, short, chunky children residing in a cool climate, while the lowest average weight has been seen in poorly nourished, cachectic, long, asthenic children, living in a warm climate. Cachexia or infectious disease of any duration or any combination of the two has been, in our experience, associated with a small gland, while we have repeatedly observed on the endocrine side a large thymus gland associated with a small or hyperplastic adrenal and a small thymus in company with normal or hyperplastic adrenal glands. There has also been a significant difference in the weights of thymus glands of similar ages in babies autopsied at the San Francisco Coroner's Office and at the San Francisco City and County Hospital. The autopsy series at the former institution includes normal children killed accidentally or murdered while in normal health, children dying suddenly from poisoning, during anesthesia, and under suspicious circumstances, and it also contains all of the cases of status thymico-lymphaticus and lymphatism included in this report, while at the San Francisco City and County Hospital the autopsies have been done on children dying of acute or chronic infectious diseases, tuberculosis, the various exanthemata, and occasional surgical and postsurgical complications. At the San Francisco Coroner's Office, the average weight of the thymus at birth has been between 4 and 20 grams; 6 to 72 grams between 6 and 12 months of age; between 6 and 45 grams at 5 years; 10 to 40 grams at 10 years; and 11 to 35 grams at puberty. We have been unable, among healthy individuals dying suddenly from trauma and autopsied at this location, to

corroborate any of the findings of the thymus from 20 years on, and in adult life, it is our experience, that the thymus is almost entirely involuted and what remains of an apparent gland at the site of the thymus anatomically turns out, upon microscopic study, to be largely areolar tissue through which are spread a very few small fields of thymic cortex with occasional involuted areas of medulla in which are rare Hassall bodies. The weight of this material, then, is not the weight of the thymus but the weight of adipose tissue in which there are a very few thymic elements. Except in status thymico-lymphaticus and disease conditions such as myasthenia gravis, dermatomyositis, and so forth, we have been unable to find any thymus remnant at all in 90 per cent of the autopsies done at the San Francisco Coroner's Office. At the San Francisco City and County Hospital the weight of the thymus in children has been much lower than that observed at the San Francisco Coroner's Office, running between 10 and 20 grams at birth, and varying between 4 and 30 grams from 5 to 10 years, 12 to 35 grams at puberty, and almost completely involuting from that time until and during adult life. These relatively lower weights are believed to be due to the lower social and nutrition levels of patients who are hospitalized in a County Hospital, plus the fact that practically all of these patients had been ill for various periods with a variety of infectious diseases.*

On the other hand, we have seen several cases at the San Francisco Coroner's Office where the thymus in normal children between 12 and 24 months of age, and killed by accidental means, has weighed between 4 and 5 grams.

With this experience in view and the wide disparity of figures of other investigators additionally in mind, it seems meaningless to speak of thymic weights as a factor of importance in diseases associated with the thymus gland unless the entire clinical picture and pathological changes in other organs are considered and correlated in addition. One cannot help speculating, however, upon the possible influence of adequate diet, both prenatal and infant, with particular reference to the vitamin supplement, on the thymic weight as observed at present. It is not outside the realm of possibility that the thymic weight observed now during the first year of life or even to puberty may be an entirely different quantity than that observed by investigators five, ten, or twenty years ago.

Part II. Experimental and Clinical Findings; Status Thymico-Lymphaticus; Theoretical Causes of Death in Lymphatism

Experimental Findings

On the experimental and brighter side, much work that has been done yields positive information. Soli[13] stated in 1910, that thymectomy in pullets would result temporarily in the laying of eggs without shell. Pigeons occasionally producing eggs deficient in shell were observed by Riddle and Křiženecký[14] at autopsy to have defective thymus glands. Dried thymus fed by him to such pigeons led to the laying of normal eggs. An experiment by Gudernatsch[15] in 1914 produced enormous tadpoles prior to their metamorphosis by feeding thymus gland. Gudernatsch felt that the thymus furnished an important growth stimulation but Uhlenhuth[16] believed, and apparently correctly concluded, that this exceptional growth was due to excellent nutrition because of the thymus diet as food. Outstanding among experiments on the thymus gland are those carried on in Asher's[17] laboratory. Nowinski[18] found an association between

*These figures are the range of weights. No averages are made.

the feeding of an aqueous extract of the thymus gland called thymocrescin and vitamin-free diet. He observed that this extract, when given daily, overcame the loss of weight in animals fed on a diet free of vitamins, that the extract stimulated growth, overcame the vitamin deficiency, and increased the size of the gonads.

In the past there has been some perceptible trend in the literature toward a belief in the endocrine character of the thymus gland and more recently numbers of reports have appeared relating the thymus to growth and reproductive processes by means of its endocrine function.

Paton[19] and Klose and Vogt[9] indicate that the thymus has a depressing action on the reproductive system. This, however, is denied by Anderson[20] who apparently has been able to show in well-controlled experiments that the thymus has no essential role in the physiology of the reproductive scheme. The inter-relation of thymus and other endocrine glands, however, is less controversial. Simon[21] in 1845 called the gland a barometer of nutrition and a very delicate one and since this time it has been known that the thymus gland responds to nutritional diseases and to many physiological conditions by involution or hypertrophy. Smith[22] showed that the thymus not only stopped growing, but that it involuted following hypophysectomy and it has been demonstrated by Uyldert and Freud[23] and Evans and associates[24] that certain fractions of the anterior pituitary containing the growth hormone cause thymus enlargement. Gonadotropic extracts from either pregnancy urine or pregnant mare serum will cause an involution of the thymus (Evans and Simpson[25]), although this effect cannot be produced in castrates. Adreno-cortico-tropic extracts have been shown to cause thymic involution as well (Moon,[26] and Credé, and Moon[27]), this effect again being obtained in both normal and castrated animals but not in adrenalectomized animals. As far as direct endocrine interrelations are concerned, Calzolari[28] first reported that gonadectomy in young animals delayed thymic involution and this has been confirmed by numerous workers since. On the other hand, the administration of sex hormone (Selye, Harlow, and Collip[29]), or physiological conditions such as pregnancy accompanied by an increased sex hormone (Schacher, Browne, and Selye[30]), result in involution noted with the onset of puberty may be due to increased production of sex hormone by the gonads under the influence of the pituitary gland.

The involution of the thymus in disease conditions of the adrenal cortex has been explained by Jaffe[31] in showing that following subtotal or total adrenalectomy, hyperplasia of the thymus as well as other lymphoid tissue would result. Andersen[32] has shown that damaging stimuli such as exhaustion, exposure to cold, starvation, various toxins, and so forth result in adrenal hyperplasia and thymic atrophy. It was Selye and associates[29] who called this the alarm reaction, and such animals are much more sensitive to toxic substances than normal animals. Ingle[33] has shown that large amounts of cortin will result in atrophy of the thymus. Since it has also been shown that administration of adreno-cortico-tropic extracts results in increased cortin production (Ingle, Moon, and Evans[34]) and since cortin causes involution of the thymus, it appears likely that in the so-called alarm syndrome, the thymic atrophy is produced by stimulation of the adrenal cortex by a principle from the pituitary gland. From the foregoing data it is apparent that there are at least two different types of endocrine influence controlling the size of the thymus, namely, a growth factor which causes enlargement of the thymus and factors (steroid substances) which cause involution of the thymus.

In 1934, Rowntree and associates[35] published an interesting review together with a report of his own experimental work with an extract of the thymus called karkinolysin which had preliminarily been prepared by Dr. Hanson for use in the treatment of cancer. Rowntree found, by injecting this material intraperitoneally daily, that in the first generation of treated test rats, the animals were heavier, bred more frequently, and had larger litters of heavier average weight than normal rats. Little of note appeared in the second generation in the first six litters cast, but in the later litters, the seventh to eleventh, precocity appeared. In the tenth and eleventh litters the animals were larger than normal, teeth erupted on the second day, and the eyes opened on the tenth day. In animals of the third to seventh generation, striking and accruing precocity, acceleration in growth and development were noted in the offspring of each successive generation under treatment. Similar effects were not observed from thymus feeding. The serum calcium in these animals was found to be increased as was the inorganic phosphorus. This suggested to Rowntree a definite bearing on the rapid skeletal development observed in the young. The hemoglobin content of the red cells and the red and white cell count showed no deviation from normal. X-rays, however, showed an increase in all dimensions in the skeletal system, particularly in the length of the diaphyses of the long bones, earlier visualization of the centers of ossification, and earlier calcification in the vertebrae. In conjunction with others he also found that large doses of this material depressed blood pressure and caused death through inducing complete auriculoventricular heart block, and he suggests that this phenomenon might possibly be of interest in relation to sudden death in status thymico-lymphaticus.

Clinical Data

Clinical studies contribute something to our knowledge of the thymus and it is now common knowledge that there is an enlargement of the thymus in exophthalmic goiter, Addison's disease, acromegaly, status thymico-lymphaticus, congenital hypoplasia of the adrenals, and anencephaly. An enlargement is occasionally seen in certain cases of myasthenia gravis, in rickets, after hypophysectomy, and after adrenalectomy. The thymus is known to be persistent in eunuchs and its involution is delayed in cases of early castration. It is small, on the other hand, in marasmus, wasting diseases, starvation, and inanition. The regression in the size of the thymus is believed by many clinical investigators to be due to the development of the reproductive organs and it has been proposed by some authorities that the enlargement in exophthalmic goiter is in the nature of a compensatory hypertrophy. Probably the most interesting of all clinical conditions is the sudden and tragic death in infants and children where a large thymus and lymphoid hyperplasia elsewhere in the body are found and because of which a diagnosis of status thymico-lymphaticus is often made.

Status Thymico-Lymphaticus

Plater[36] in 1614 described a condition "mors thymica" caused by pressure of the thymus on the trachea. Friedleben[4] by 1855, however, was of the opinion that there was no causal relationship between an enlarged thymus and sudden death. Paltauf[37] described a series of five cases of death resulting from minor trauma. He found the thymus and other lymphoid tissue to be hyperplastic. He also described asthmatic tendencies in children in this series, with subpleural petechial hemorrhages and pulmonary edema. Three of the

five cases also had aortic hypoplasia. He considered these individuals as having a constitutional weakness, rendering them more susceptible to death from trivial injuries. Status thymico-lymphaticus was also described by Osler[38] who defined it as "a condition in childhood of hyperplasia of lymphatic tissues and of the thymus in association with a flabby fat overgrowth of the body and hypoplasia of the heart and blood vessels. Pathological examination in his experience disclosed overgrowth of the bodies and relatively large heads, hyperplasia of the lymph glands and structures of the tonsillar ring, moderate enlargement of the external and internal lymph glands, and hyperplasia of the solitary and agminated follicles of the small and large intestine, and atrophy of the adrenals. The thymus was enlarged, swollen and soft, and bone marrow was hyperplastic and in young adults the yellow was replaced by red marrow; a small heart and small aorta and peripheral vessels were found at times and there was often associated condition of rickets. What has called special attention to this condition is the tragedy of sudden death following trifling causes, a prick of a hypodermic needle, a sudden plunge in cold water, but more often in anesthesia, either ether or chloroform, when an amount has been given not in itself lethal."

Theoretical Causes of Death in Lymphatism

Two basic explanations have been advanced by many authors for the thymic death, namely, the mechanical and the hormonic, while others cast doubt upon the very existence of the syndrome, stating that the sudden death characterizing this condition had never been proved to be due to lymphatism, mechanical factors, endocrine upsets, allergy, asthma, or an excess of secretion, associated with the thymus gland.

As opposed to the opinions of Young and Turnbull,[11] Bratton,[39] Hammar,[8] Boyd,[40] Kennedy and New,[41] and others that the thymus or enlargement of the thymus can seldom or never be established as a cause of death, Paltauf[37] has numerous supporters. Symmers[42] has defined a status lymphaticus in which he apparently believes, and considers it to be an actual constitutional disease.

In a theorem of the cause of death in status lymphaticus, listed in chronological sequence, are: (1) Mechanical obstruction, first proposed by Plater.[36] It is interesting today that this idea has very little evidence in its favor. Boyd[40] concedes that it is an anatomical possibility because of the relationship of the thymus to great vessels and the recurrent laryngeal nerve. Pressure upon these is just as likely a possibility as pressure upon the trachea itself.

(2) Thymic lymph toxin. This idea was based on Svelha's[43] studies in which he showed that injections of thymus extract cause the picture of shock in animals and death has been proved to be due to the presence of nonspecific protein particles in the extract.

(3) Anaphylaxis. Symmers[42] reported that in cases of thymic death both thymus and lymphoid tissues were hyperplastic microscopically as well as grossly and that numerous areas of necrosis were present in the germinal follicles in the lymph nodes from anaphylaxis caused by the liberation of nucleoprotein from lymph nodes. Waldbott and Anthony[44] also believe that allergic manifestations were very frequent in children with a lymphatic constitution. In a study of thirty cases in which the thymus was found to be large by x-ray, a very high percentage of these cases gave positive histories of allergy in the form of skin, respiratory tract, or gastrointestinal tract manifestations. Waldbott[45] studied a series of thirty-four cases which had been diagnosed as thymic

death. He was able to confirm Symmers in the histopathology of lymph nodes in thymic deaths. In addition he described congestion, edema, atelectatic areas, and emphysematous areas in the lung. He believed the pathology was essentially that of anaphylaxis.

(4) Adrenal insufficiency. Greenwood and Woods[46] define status thymico-lymphaticus as a constitutional defect, agreeing with Symmers. Hypoplasia of the adrenal medulla as well as the cortex has been reported frequently, not only by Marine,[48] but also by Wiesel[49] and the similarity between Addison's disease and status lymphaticus in regard to the size of the thymus and the increased susceptibility to toxic agents has been commented upon. The experimental production of status lymphaticus by partial supra-adrenalectomy has been reported upon by Crowe and Wislocki,[50] Marine and his co-workers,[51] and Jaffe.[31] Marine was of the opinion that adrenal cortical insufficiency might result from postnatal involution and both thymic and lymphatic changes. Kemp[52] is also of the belief that adrenal cortical insufficiency is present in status thymico-lymphaticus, and those believing in the allergy theory as a cause of death cite the following criteria:

1. A history of allergy with cyanosis and dyspnea
2. Physical findings of allergic manifestations and an impaired nutritional status
3. Anatomical findings by x-ray or at necropsy of an enlarged thymus with degenerative changes in the thymus and lymph nodes, evidence of allergy with edema, petechial hemorrhages and skin lesions, and possibly hypoplasia of the aorta and adrenal glands*

Part of the confusion existing in the literature and in the minds of doctors today is perhaps due to a futile ambition to ascribe all deaths in children with lymphatism to one cause. Certainly there is enough material available in the literature to certify that sudden death does occur in this condition with no cytological changes being demonstrable at autopsy other than hyperplasia of the lymphatic tissues and enlargement of the thymus. That not all of these cases point to a common cause of death is, however, equally true, which may mean that at least some and possibly all of the theories of death in lymphatism which we have enumerated are valuable and that the diagnosis of lymphatism should not only not be discarded as both a clinical and necropsy diagnosis but rather could with profit be broadened and extended with qualifications added covering the conditions which upon analysis prove to be more than pure theory.

Part III. Segregation of Case Types; Status Thymico-Asthmaticus; The Mechanism of Strangulation in Enlargement of the Thymus

Segregation of Case Types

In the past six years at the San Francisco Coroner's Office, we have seen 520 cases of sudden death in children below 10 years of age. Eliminating accidents, infections, postoperative complications, congenital anomalies other than those of the lymphatic system, inanition, malnutrition, poisoning, tumors, burns, heart disease, hemorrhage and diabetes, bring this total down to 105 children in this age group who died suddenly and apparently of suffocation. Eliminated from this group also are stillbirths, premature infants, and babies

*Hasley,[53] by correlating pictures with autopsy findings, has demonstrated that the thymus shadow in x-ray is not a reliable index of the size of the thymus, but he believes that the cyanosis or stridor associated with the presence of a thymus shadow on x-ray is an indication for x-ray therapy.

dying within twenty-four hours after delivery. To further separate this group into groups dying from suffocation by strangulation and mechanical obstruction without lymphatism and those having anatomically proved lymphatism becomes a critical problem, but of this total we can collect 49 cases dying of conditions arising from, or directly associated with, pathological changes in the thymus and lymphatic system. This group offers what we feel to be indisputable examples of death from asphyxia following tracheal compression from an enlarged thymus gland, deaths from partial obstruction by an enlarged thymus during or following anesthesia, cases showing a combination of thymic enlargement, lymphatism, and anaphylaxis, and substantiated cases of adrenal insufficiency associated with thymic hyperplasia. There are several examples of the reverse of this condition with adrenal enlargement and hypoplasia of the thymus in which death has occurred suddenly and with no other positive findings than those. It is not possible in this series to report any true examples of death directly or indirectly from thymic lymph toxin but we can report cases dying from a hypoplasia of the thymus with hyperinvolution, medullary atrophy and degeneration of the Hassall bodies, in which there have been some toxic manifestations.

Fig. 2.—Very large thymus covering upper two-thirds of heart.

Status Thymico-Asthmaticus

In addition to reporting a series of cases of each of these types, we wish to contribute a new descriptive term which denotes a disease entity frequently responsible for strangulation in the young, namely, status thymico-asthmaticus. Under this heading is presented a series of cases occurring in widely varying age groups where death has occurred from asphyxia and wherein the thymus is enlarged. This enlargement is of lesser degree than in cases dying with acute tracheal compression from an enlarged thymus and associated with it is an hyperplasia of the lymphoid system which instead of being generalized is limited largely to the bronchi and bronchioles. Because the lymphocytic infiltration is in the submucosa, and among the muscle fibrils

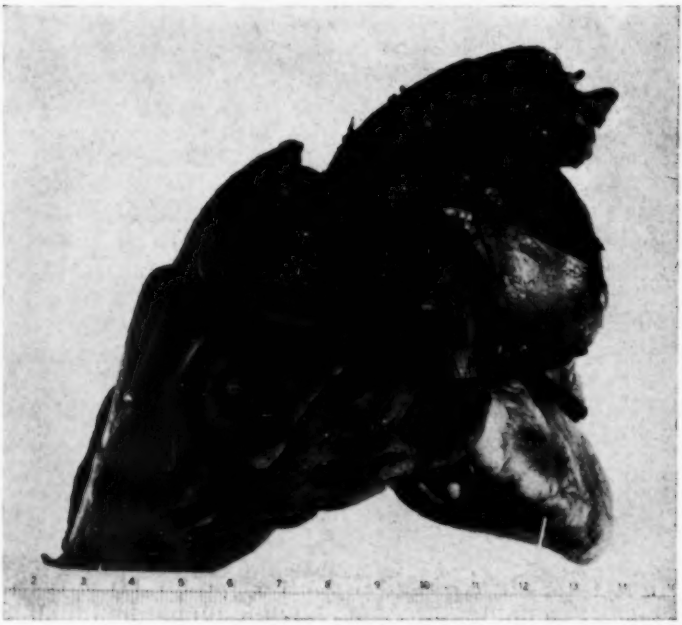

Fig. 3.—Showing compression and backward curvature of trachea. Note large tracheal nodes and subpleural hemorrhages of asphyxia.

Fig. 4.—Lateral view showing displacement of heart and lungs by large thymus.

Fig. 5.

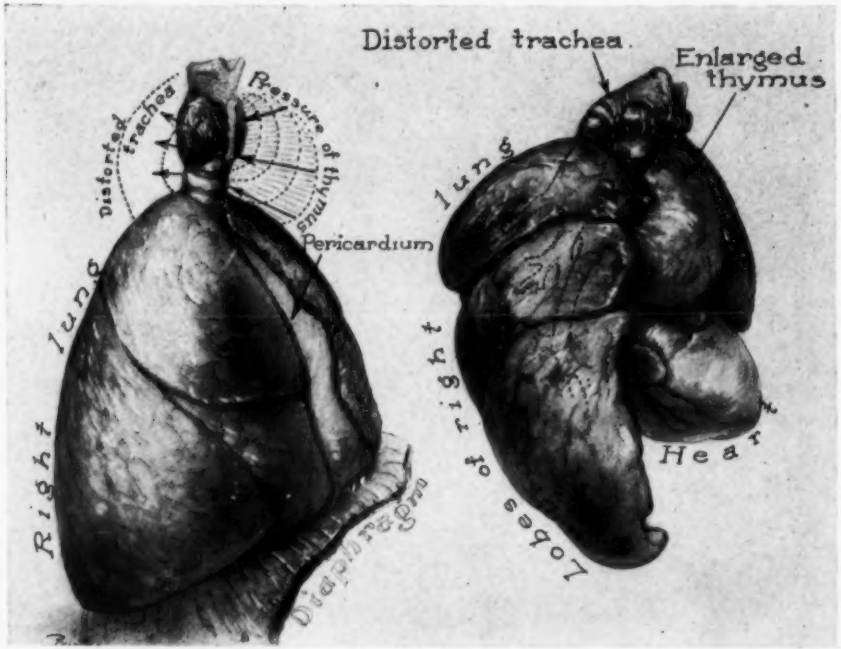

Fig. 5-A.

Fig. 5.—Apices are pulled downward, the bases are thrust upward and forward by backward pressure of the large thymus. Note subpleural and epicardial hemorrhages of asphyxia.

Fig. 5-A.—Comparative sketches of normal thoracic contents and of specimen in Fig. 3, showing dynamics of displacement and rotation.

as well as peribronchial, the term asthmaticus is included. This picture cytologically resembles a developing or existing asthma and the clinical course is differentiated with difficulty from true asthma excepting for the single but very important fact that the status thymico-asthmaticus group show no beneficial response to the injection of epinephrine.

There is previous justification in the literature for combining the terms asthma and status thymico-lymphaticus. Waldbott[54] in 1935 described two cases of asthma in infants. The autopsy protocols done by Dr. A. C. Edwards referred to peribronchial and peribronchiolar lymphocytes which were regarded at this time as part of the cellular infiltration in asthma or as a

Fig. 6A.—Anterior view showing large thymus causing inferior displacement of heart with posterior and lateral displacement of lungs. Note subpleural and subepicardial hemorrhages.

response to an allergic manifestation. Considering pathological changes which had been previously described in so-called thymic death and allergic shock, Waldbott indicated at this time that he thought it possible that these conditions might be equivalents. Other reports of death from asthma or asthmatic conditions in infants are rare. In 1931, Coca, Walzer, and Thommen[55] recorded in their summary of the literature on 33 deaths from asthma, the cases of only two children, aged 2 years and 15 months, respectively. In the case of five months' duration, the diagnosis of bronchial asthma was questioned because of the presence of a large thymus and other characteristics of status thymico-lymphaticus. MacDonald[56] has reported one case of a 13-year-old girl which he added to about 15 other additional records which he was able to collect, but at the Children's Hospital of Michigan only one case of death from asthma in a child was reported in the records of 819 autopsies. At the Children's Memorial

Hospital in Chicago one case of asthma in children was reported by Huber and Koessler[57] in 1922, while at the University of Michigan Hospital from 4,000 pathological records since 1896, no report of a case of asthma in a child under 10 years of age has been made. Similarly at the Harper Hospital in Detroit no record of a case of death from asthma in an infant or child was found in 259 autopsy reports.

Mechanics of Strangulation in Hypertrophy of the Thymus

Enlargement of the thymus alone can, in specific instances, so disturb the physical dynamics of the chest to cause death. Enlarging as it does from birth to puberty, an abnormally large gland first extends downward over, and frequently covering, the auricles of the heart (Fig. 2). With downward growth

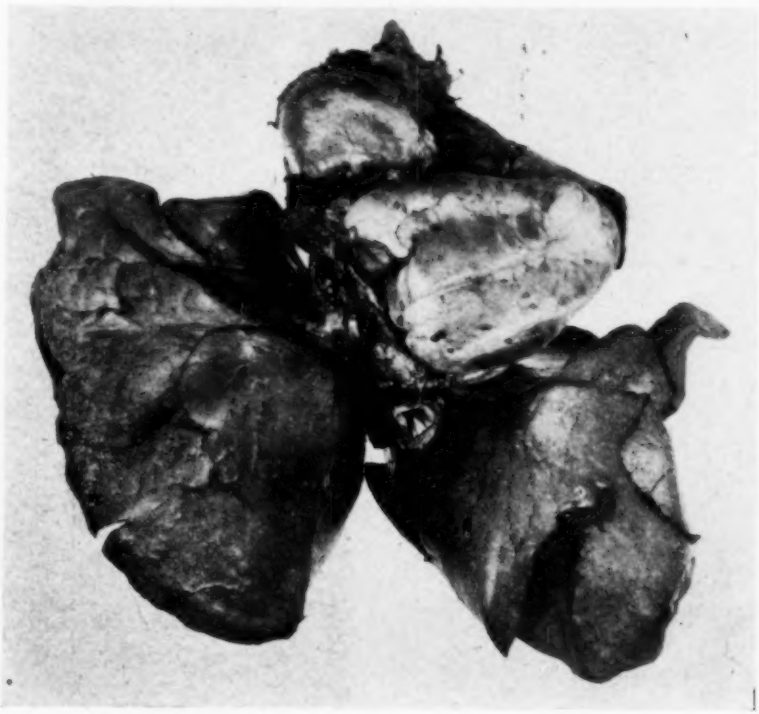

Fig. 6B.—Heart rotated cephalad showing subpleural and subepicardial petechial hemorrhages of asphyxia.

further obstructed by the mediastinal contents, increase in size causes a backward curvature of the trachea from the larynx to the trachea bifurcation. The trachea is flattened in an anteroposterior position, the size of the lumen is reduced and the entire tube is foreshortened (Fig. 3). Together with these changes, the roots of the lungs are pulled upward and gradually thrust forward forcing the lungs to rotate on a lateral axis running through either hilum from side to side, finally assuming a position in which the bases face downward and forward approximately toward the costal margins. The apices are pulled down below the clavicles and the middle portions of pulmonary parenchyma are thrust laterally and backward against the thoracic wall (Fig. 4) and (Fig. 5). With this position assumed, each contraction of the diaphragm results in

an abnormal pulmonary excursion with the backs of the lower and middle lobes migrating downward while the bases more forward; with each respiratory movement the trachea is then pulled downward further compressing it against the large mass of thymus in the upper mediastinum. Each inspiration then causes a partial occlusion of the lumen of the trachea at the point where

Fig. 7.—Mature Hassall bodies in a normally involuted thymus.

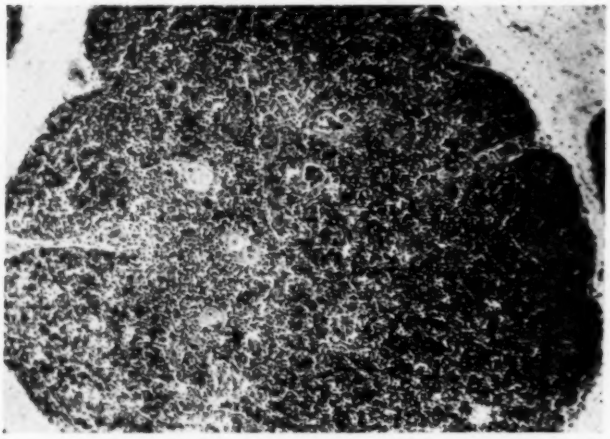

Fig. 8.—Medullary involution is accompanied by replacement of the Hassall bodies by inflammatory cells in the right half of the medullary zone.

it arches behind the thymus gland with an apparently delicate balance existing between a normal respiratory exchange and partial asphyxia. As in the case of asphyxia from other causes, some trigger mechanism, such as anesthesia, aspiration of formula and other foreign substance, or infection stimulates the respiratory rate or the oxygen demand and with increased ventilation, irritation, mucous secretion, and beginning edema of larynx, trachea, and thymus, strangulation is initiated. At this same time lateral and superior pressure upon the heart by the thymus interferes with proper filling of the auricles with a resulting pulmonary congestion. The progression from strangulation to as-

phyxia is in our experience extremely rapid from any cause and once started a secondary sequence of bronchial spasm and rapid mucous secretion adds to an already beginning dyspnea. Death ensues from strangulation and asphyxia, there is acute congestion of the viscera, and the petechial hemorrhages of asphyxia are found beneath the visceral pleura, the pericardium, the capsule of the thymus, the gland itself, the lungs (Fig. 6), and frequently in the brain stem.

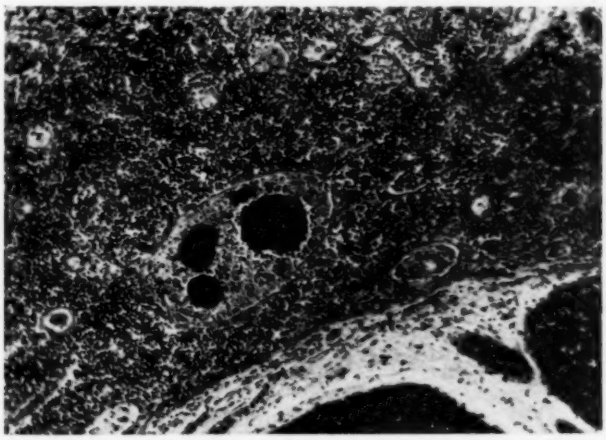

Fig. 9.—Completely degenerated Hassall body beginning to fragment.

Case Reports

Group One: Asphyxia Due to Tracheal Obstruction and Displacement of the Heart and Lungs by an Enlarged Thymus With and Without Hypoplasia of the Adrenal Gland

Case 1.—Baby L. This 7-week-old male baby had been a normal delivery after a term pregnancy. He had been taken care of by his parents and had been normal since birth. There never had been attacks of dyspnea or cyanosis. It was the custom of the baby's mother to have a nurse come in during the day to take care of the baby and on March 6, 1941, approximately at noon, the nurse put the baby into a buggy on the porch. She looked at him at 1:20 P.M. and saw blood coming from his nose. He was lifted from the buggy and appeared very limp. She did not notice at this time whether he was breathing. The Emergency Service was called and he was taken in an ambulance to the Alemany Emergency Hospital where he was dead on arrival at 1:35 P.M. The mattress on the baby buggy was firm and there were no feather pillows or blankets bundled up in the crib.

Autopsy Findings

There is a sanguineous, frothy fluid in the nostrils and a well-developed post-mortem lividity posteriorly. The development of the child is normal, nourishment appears adequate, and there are no other distinguishing marks on the body.

The thymus, trachea, heart, and lungs are all dissected out in a block (Fig. 4). The lungs show many small petechial hemorrhages scattered throughout, both subpleural and in the pulmonary parenchyma and there are also numerous subepicardial petechiae (Fig. 6). The thymus is enlarged and the lobes are symmetrical. It weighs approximately 30 grams and measures 5 by 2.5 by 3 cm. for the right lobe and 3 by 3 by 4.5 cm. for the left. The lobes meet in the midline and reach downward completely covering the auricles of the heart. The left lower margin of the thymus is down to the mid-portion of the ventricle on the left side, being only 2.5 cm. above the apex. This large thymic mass pushes the trachea backwards and the trachea now curves from the roots of the lungs upwards, backwards, and then arches behind the thymus to project forward, presenting itself in an almost horizontal plane, facing forward over the upper poles of the thymus gland.

The heart is displaced downward and rotated on a transverse axis, the apex now facing almost forward toward the anterior surface of the chest cavity, and the lungs are pushed backward and rotated about 30 degrees through a horizontal axis in a lateral plane running through the level of the hilus. The inferior margins of the lower lobes now face forward toward the anterior rib cage instead of toward the diaphragm.

The liver is rather pale and yellow but is otherwise normal.

The spleen weighs 16 grams, shows a rather pale pulp and the lymphoid follicles are large and prominent.

The kidneys are fused together in the midline at the upper pole and present a horseshoe shape, but drain by independent ureters, and weigh a total of 59 grams. Over the upper pole on either side there is an adrenal gland which is smaller than normal and which, on cut section, shows an extremely thin cortex that is less than 1 mm. across. Medullary elements are also extremely thin but there is no adrenal hemorrhage. The kidney parenchyma is normal but there is still prominent fetal lobulation.

The bladder and prostate are normal, as is the gastrointestinal tract.

The brain is within normal limits excepting for a moderate edema.

Microscopic Examination.—Sections of the organs are normal excepting for the petechial hemorrhages in the lungs, epicardium, and underneath the pleura.

Sections are made also of the pituitary and pineal glands which show no pathological changes.

The thymus shows well-differentiated cortical and medullary zones which are thick and composed of normal cells. The Hassall bodies show no degeneration.

Diagnosis

Asphyxia following tracheal distortion and compression of the trachea and auricles by an enlarged thymus

Subpleural, subepicardial, and pulmonary petechial hemorrhages

Hypoplasia of the adrenal glands

CASE 2.—A. D. This patient was a normal, 3-month-old girl, who had been delivered at term without forceps from a normal intrauterine position. There was no clinical history of feeding difficulties, cyanosis, symptoms of circulatory distress, or of tracheal and bronchial obstruction. The baby was normal, according to the mother, and on March 30, 1942, at 9 A.M., the baby's mother left her lying comfortably in the crib. Forty minutes later she entered the nursery room and found the baby lying crosswise in the middle of the crib, face down, underneath the three light baby blankets which were on the bed. She was not particularly discolored at this time, although a little blue, and the mother took her immediately to the Mission Emergency Hospital where she was pronounced dead on arrival. The covers were loose and not held down tightly over the child. The mattress was of silk floss covered with a rubber sheet and there was no pillow.

Autopsy Findings

External examination shows a well-nourished, white, female infant, approximately 3 months of age. There is a slight dependent lividity and a very little rigor mortis. The head, eyes, ears, nose, and throat are normal. There are no developmental anomalies.

The scalp and meninges are intact and normal. The brain weighs 700 grams and shows slightly flattened convolutions due to edema. Sections through the brain show normal structures.

The heart is normal in size, shape, and configuration. Upon opening the heart, the muscle and coronary system show no pathological or developmental changes. The foramen ovale is still partially open and the ductus arteriosus still exists as a small cord through which there is an opening of approximately 0.5 mm. in diameter.

The lungs show normal pleural surfaces and a normal circulatory and bronchial arrangement at either hilus. They are dissected out in a block with the thymus and heart, and upon being removed from the chest are found to have been rotated backward in a lateral axis with the middle portions of the lungs on either side being compressed against the posterior chest wall. The inferior margins of the lungs have been thrown forward and the apices curve forward together with the trachea over the enlarged thymus gland.

The thymus is extremely large, approximately three times the size of the heart, measures 7 by 7 by 3 cm., and weighs 52 grams. Upon looking at the thymus from the anterior aspect, only 1.7 cm. of the apex of the heart are visible below the lower margin of the fissure of the thymus between the two lobes (Fig. 2). The lobes are nearly symmetrical and sections through them show a normal structure.

The spleen is moderately congested, but is small, weighing only 9 grams. The capsule is stretched rather tightly due to the congestion. Sections through the spleen show very indistinct lymphoid follicles, a normal pulp and a normal circulatory system at the hilus. The spleen measures 2.5 by 5 by 1.3 cm.

The kidneys weigh approximately 20 grams apiece and over the top of each kidney is a very tiny adrenal gland. The kidneys still show fetal lobulations and the capsules strip away readily leaving smooth renal surfaces. Sections through the kidneys show them to be normal.

The adrenals, upon section, show a cortex which in either layer is less than 1 mm. in diameter and between the layers of cortex runs only a very fine brown line of medulla (Fig. 10). After dissecting away the areolar tissue covering the adrenals, the left is found to weigh 900 mg. and the right 860 mg.

Fig. 10.—Adrenal hypoplasia with very thin cortices and scant medulla. Note the small adenoma.

The kidneys drain through normal ureters into a bladder which is practically empty but normal.

The uterus, tubes, and ovaries are normal.

No pathological changes are found in the gastrointestinal tract.

Microscopic sections are taken of all the organs.

Microscopic Examination.—Microscopic examination of the tissue sections shows all of the organs to be within normal cytological limits excepting for the brain where there are very fine petechial hemorrhages in the leptomeninges consistent with asphyxia. Cytologically the thymus sections are normal, although there is far more tissue than in the normal thymus. Sections of the adrenal glands show an extremely thin cortex, but the glomerular, reticular, and the fasicular zones are clearly differentiated and there is very little lipoid in the cells. The medulla is also greatly reduced in volume and there are only four or five cells in any section separating the two layers of the cortex. There is still a heavy deposit of glycogen in the cytoplasm of the cells of the liver.

Diagnosis

Hypertrophy of the thymus
Asphyxia from tracheal compression and distortion
Hypoplasia of the adrenal glands
Petechial hemorrhages of the leptomeninges

CASE 3.—J. N. R. This 4-month-old male infant was a normal full-term delivery and had been under the care of the Well Baby Division of the Telegraph Hill Clinic since birth. In January, 1941, at the age of 2 months, it was noted that he had a little respiratory difficulty, some obstruction of his trachea, and a rather hoarse cry. An x-ray of the thymus was advised at this time but was never taken. In February, at the age of 3 months, the baby was

returned to the clinic for examination where he was put on a formula and vegetables added to the diet, but no note was made at this time of his respiratory difficulty. On March 4, 1941, the baby was again seen at the clinic. The respiratory difficulty had returned, and the mother was advised to take the baby to the San Francisco Hospital that afternoon for an x-ray of the thymus and chest. The baby was taken from the clinic at 1:15 P.M. and placed on his back in a bassinet by the mother. He was then left in care of a nurse who went up on the roof for not more than ten minutes to hang up some clothing. She returned to find the baby lying on his face and apparently not breathing. She rushed him back to the clinic where he was examined and pronounced dead at 2 P.M., forty-five minutes after his examination. Artificial respiration was attempted, assisted by an Emergency Service pulmotor, but with no beneficial result. Obviously, and from the medicolegal aspect very fortunately, the chest plate advised that morning was never taken.

Autopsy Findings

External examination shows a well-developed, but only fairly well-nourished child with a rather marked post-mortem lividity. There are no petechial hemorrhages about the sclerae and conjuntivae and no surface marks of distinction are seen.

The lungs are aerated. There are a few small, petechial hemorrhages beneath the pleura and these hemorrhages are also found throughout the pulmonary parenchyma. There are numerous fine petechial hemorrhages underneath the epicardium, but none are found elsewhere. The lungs and heart are dissected out in block together with the thymus, which is large. The gland weighs 34 grams, covers both auricles of the heart, and extends halfway down over the left ventricle to within 2.2 cm. of the apex. This thymic mass compresses the trachea, pushing it backward into an arch curving through approximately 180 degrees. The pulmonary lobes are displaced laterally and the heart is forced downward. Upon opening the heart, no congenital anomalies are found and the foramen ovale and ductus arteriosus are closed.

The adrenals are small and show extremely thin cortical zones. There is no medullary hemorrhage, but the medullary zone of cells can barely be seen grossly.

The brain shows a moderate edema but is otherwise normal and no pathological changes are found in any of the other organs.

Microscopic Examination.—

Lungs: The lungs show a normally aerated pulmonary parenchyma. There is no consolidation or atelectasis. The bronchial channels are open, contain no mucus, and about them there are no peribronchial lymphocytic infiltrations or evidences of hypertrophy of the bronchial musculature.

Thymus: There is an extraordinary development of both cortex and medulla which are thicker than normal and in the medulla the Hassall bodies are well developed, mature, keratinizing, and show no central degeneration. Throughout the thymus and lungs and beneath the epicardium and visceral pleura are numerous small petechial hemorrhages, such as are seen in asphyxia.

Adrenals: The adrenal zones are extremely thin and both sides of the cortex can be gotten in a high-power microscopic field. The cells, however, are normal and there is lipoid in the cortical areas. The medullary areas are also very thin but no cytological changes are found.

Heart, Liver, Spleen, Pancreas, Kidneys, Bladder, Prostate, Gastrointestinal Tract and Brain: These organs show no microscopic changes in the sections.

Diagnosis

Asphyxia following tracheal distortion and compression by an enlarged thymus gland
Subpleural, subepicardial, and pulmonary petechial hemorrhages
Hypoplasia of the adrenal glands

CASE 4.—P. D. This baby, a 3-month-old girl, was born at term after a normal pregnancy, there being no reported unusual circumstances attending the birth or the post-natal life of the baby until 7 P.M. on Dec. 14, 1939. At this time the parents put the baby in her crib, covered her with the usual bed clothing, and went to a theater leaving the baby home alone. They returned two and one-half hours later at 9:30 P.M. and both retired without seeing the baby. At 10 P.M., three hours after seeing the child well and alive, the mother arose to give the baby her ten o'clock bottle and upon going to the crib found the infant lying face downward, but in the same position as that in which she had been put in the crib and apparently suffocated. The Central Emergency Hospital ambulance was called immediately and the baby was pronounced dead by the ambulance steward at 10:30 P.M. According to

the parents, they did not look at the baby at 9:30 P.M. when they returned from the theater because they thought that the baby was asleep and did not wish to disturb her. There was a fairly well-developed post-mortem rigidity of the body when the deputy coroner arrived at 11:50 P.M. According to the parents there had never been any feeding difficulty, episodes of cyanosis or dyspnea or any other untoward or unusual circumstance attending the normal and routine life of the infant.

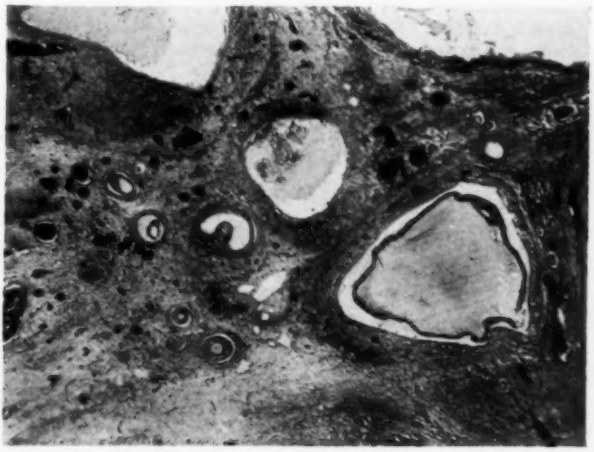

Fig. 11.—Maturing follicles and small follicular cysts appearing at 4 months of age.

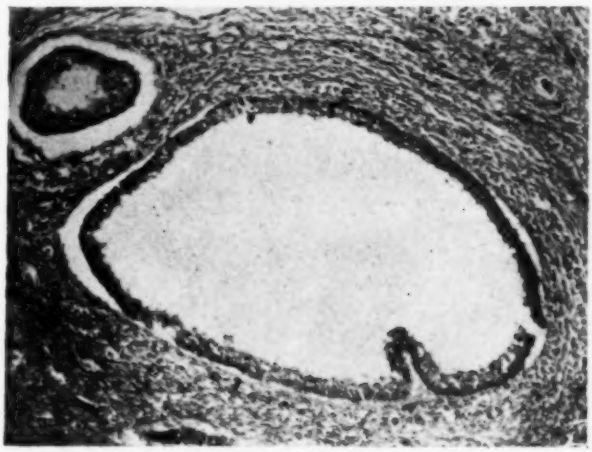

Fig. 12.—Follicular cyst in a 3-month-old baby girl with enlarged thymus gland and death from asphyxia.

Autopsy Findings

External examination of the baby shows a well-developed and nourished baby girl, moderately livid in the dependent portions of the body and still quite rigid. The development is normal and there are no congenital anomalies. The extremities are symmetrical and well formed and the external genitalia are normal. There are no evidences of violence or injury on the body.

The scalp, skull, and the meninges are normal and the brain shows only a little edema. Sections through the brain show symmetrical, normal ventricles and no pathological changes.

The lungs are removed in a block together with the heart and thymus. They have normal pleural surfaces and a normal circulatory and bronchial arrangement on either side, but they

are displaced backward in the chest and the lower margins are projected forward due to compensatory movement of the lower portions of the lungs, from backward displacement of the middle of the parenchyma by an enlarged thymus. There is an anterior rotation of the apices and of the trachea which bends forward over the posterior face of the thymus gland. The lungs appear atelectatic and there are many subpleural petechiae with a frothy exudate in the minor bronchi. There is no purulent consolidation. These organs are preserved intact for museum display. The thymus is not weighed.

The heart is normal in size, shape, and contour and beneath the pericardium there are a few very fine petechial hemorrhages. The myocardium and coronary system appear normal. The aorta is of normal caliber; the foramen ovale is closed, and the ductus arteriosus is no longer patent.

The liver is rather congested, brownish-purple in color, has a normal surface, a sharp edge, and a normal extrahepatic biliary system. Sections through it show a normal structure.

The spleen is of normal size, shows a moderate congestion of the pulp, and the lymphoid follicles are barely visible.

The pancreas, kidneys, and adrenal glands are normal.

The uterus, tubes, and ovaries are normal excepting for an approximately 50 per cent enlargement of the ovaries on both sides, which upon section are found to contain many small cysts running from 1 to 2 mm. in diameter which are supported by a dense ovarian stroma.

The urinary bladder contains about 4 c.c. of urine and is grossly normal.

No pathological changes are seen in the gastrointestinal tract.

Microscopic sections are taken of all the organs.

Microscopic Examination.—Microscopic sections show an acute congestion of the lungs, liver, and spleen, while beneath the pleura and pericardium there are many fresh points of hemorrhage. These are either petechial or a little larger in character and are fresh. Some of the alveolar spaces are collapsed and contain very little air, but there is no consolidation. There is no bronchial or peribronchial lymphocytic infiltration.

The other tissues are within normal cytological limits, excepting the ovaries where the cysts, described grossly, are found to be lined with a single layer of flat or cuboidal epithelium and filled with a coagulated protein debris which stains pink with eosin. There are many germinal follicles in the ovarian parenchyma (Figs. 11 and 12).

Sections of the thymus show normal cortical and medullary areas with many well-developed Hassall bodies in the medulla.

Diagnosis

Asphyxia from tracheal distortion and compression by an enlarged thymus
Subpleural and subepicardial petechial hemorrhages. Pulmonary atelectasis
Congenital ovarian cysts

CASE 5.—G. D. C. This baby, a 4-month-old boy, was a normal term delivery. He was taken off the breast the first week of his life and given a bottle formula which was well taken and which caused no distress. There was no evidence of allergy or other clinical difficulty and the child never showed any evidences of respiratory obstruction or cyanosis. There were no developmental anomalies. He was attended by his mother at 11:20 A.M. on July 7, 1940, and after being made comfortable in his crib, was left lying on his stomach which was a usual position while his mother went to prepare a bottle. At 11:30 A.M., she returned with the bottle and found him still face down in the crib apparently dead. The mattress was a kapok mattress covered with a rubber sheet and a cotton sheet. There was no pillow in the crib and the baby's head was not covered with bedding. The Emergency Service was called and the baby was pronounced dead at 11:50 A.M. by the emergency steward.

Autopsy Findings

There is a moderate post-mortem rigidity and a little increased post-mortem lividity. The color is deeply cyanotic. The baby is well nourished and otherwise appears normal.

Upon opening the thoracic cavity, both lungs are found to be moderately atelectatic but lie in clean pleural cavities and are somewhat displaced laterally and posteriorly by an exceptionally large thymus which nearly covers the entire anterior cardiac surface. Upon removal the lungs show normal circulatory and bronchial channels on either side, but as they are dissected out in a block with the heart and the thymus, the middle portions are seen to be displaced laterally and posteriorly, throwing the bases of the lungs upward and forward and causing a forward curvature of the apices together with the trachea over the top of the thymus gland.

The heart is normal in size, shape, position, and development. The foramen ovale and the ductus arteriosus are closed.

The thymus weighs 42 grams and measures 7 by 7 by 3 cm. The lobes are symmetrical and sections through the thymus show a little brown degeneration of the medulla which is apparently post mortem, but the structure is otherwise within normal limits.

All of the other organs, including the brain and pituitary, are normal. Multiple microscopic sections are taken.

Microscopic Examination.—

Thymus: Sections of the thymus show a well-differentiated cortex and medulla and mature Hassall bodies with large areas of central keratinization. There is no degeneration.

Lungs: Throughout the lungs, the alveolar spaces show some collapse. This atelectasis is incomplete but general. There is acute congestion of the circulatory channels of the alveolar walls, but there is no consolidation. No subpleural hemorrhages are seen.

Heart: Sections of the heart muscle are within normal limits.

Adrenals: Microscopic sections of the adrenal glands show normal cortical and medullary zones and a plentiful supply of lipoid in the cortical cells.

Diagnosis

Asphyxia and acute pulmonary atelectasis, following tracheal distortion and compression by an enlarged thymus

CASE 6.—R. G. The subject is a 9-month-old male baby, who had had a normal delivery and who had been a child of normal development, never having had any apparent respiratory difficulty before the present attack. He had not been a feeding problem and had never had eczema or other allergic manifestations. On Feb. 29, 1940, at 2:30 P.M., the baby awoke from a nap in his buggy with a croupy cough. His mother felt that he might have aspirated a bug while asleep and called her family doctor approximately four hours later. The doctor responded immediately and found the child coughing and breathing with some difficulty. He took the baby to the hospital where a bronchoscope was passed at 8:50 P.M. No foreign body was found upon bronchoscopy, although the bronchoscope was passed with some difficulty owing to the curvature of the trachea. The respiratory difficulty increased during the night and the baby died from asphyxia at 7:30 A.M. on March 1.

Autopsy Findings

External examination of the baby shows a red staining by dye in the upper part of the chest and neck which is part of the preoperative preparation. The skull is symmetrical and well formed. The eyes, ears, nose, and mouth are normal. The nutrition is good. The baby is 2 feet, 6 inches, in length and weighs 24 pounds.

Upon lifting off the thoracic cage the lungs appear normal except for dark purplish-red discoloration of the right upper lobe of the lung and many subpleural petechial hemorrhages. There are five lobes on the right side (Fig. 3). There are also many subepicardial petechial hemorrhages (Fig. 3) and the heart is pushed down by a very large thymus which measures 8 by 6 by 4 cm. (Fig. 6). This gland almost completely covers the entire heart compressing the auricles and presses the trachea sharply backward, causing it to curve an arc of nearly 180° in running from the larynx to its bifurcation at the roots of the lungs (Fig. 3). The thymus also presses upon both upper and right middle pulmonary lobes and forces the lungs into a rotation on a transverse axis through the roots of the lungs, throwing the apices backward and the lower lobes forward with the bases facing almost directly anteriorly. There is a hyperplasia of all of the lymph nodes on either side of the trachea in the vertical chain and there is a complete collapse of the right upper pulmonary lobe in which there is a little free blood. Sections through the lungs show them to be aerated excepting for the right upper lobe and there is no evidence of consolidation, mucus, blood in the bronchi, or of foreign bodies in the respiratory tree. These organs are preserved intact for a museum specimen. The thymus is not weighed.

Upon opening the heart, normal valves, epicardium, pericardium, muscle and coronary circulation are found, and the aorta arches from the ring upward and around in a normal fashion excepting that it is pressed downward to some degree by the thymic mass.

The liver is normal.

The spleen weighs 22 grams and shows a moderate congestion with prominent lymphoid follicles, but shows no other pathological changes. The follicles are no larger than those usually seen in a baby of this age.

The adrenals are very small for this age and show an extremely thin cortex on either side with practically no medulla. They weigh 1.6 and 2.0 grams for right and left, respectively.

The pancreas is normal.

The kidneys are normal, show fetal lobulations, and drain through normal ureters into a bladder which is empty.

Upon lifting off the cranial cap, a moderate edema of the brain is seen, but the brain is otherwise normal throughout.

Microscopic Examination.—

Heart: Sections show normal pericardium and muscle. There are many subepicardial hemorrhages which are fresh.

Lungs: The lungs are aerated and show no consolidation, but sections taken of the right upper lobe show an atelectasis with a few red cells in some of the alveolar spaces. No areas of emphysema are found. About the bronchiolar channels and bronchi as well, there is a diffuse infiltration with lymphocytes and the nodes at either hilum are extremely large and hyperplastic. This chain of lymphatic tissue apparently runs from the major bronchi down along the minor bronchi and about the bronchioles where there are frequent nests of lymphocytes running down even to the terminal bronchioles where they emerge into the alveolar spaces. Along these lesser bronchial and bronchiolar channels there are no follicles in the lymphoid element and no germinal nodes are found.

Thymus: The thymus shows an extremely thick cortical zone with no apparent involution and in the medullary areas there are the usual number of Hassall bodies with well keratinized centers. There is no liquefaction or degeneration of the medullary areas or of Hassall's corpuscles.

Liver: The liver shows a moderate cloudy swelling of the cytoplasm of the cells and there is no glycogen storage.

Spleen: The spleen shows closely-placed corpuscles with hyperplastic centers and a moderate congestion of the pulp with erythrocytes.

Pancreas: The islets and acini are normal.

Adrenals: The cortical zones are thin, poorly differentiated, and most of the cells are from the glomerular layers. The medullae are only 6 to 8 cells thick and the cells are small and hyperchromatic.

Kidneys: The glomeruli and tubules are normal. The pelvic membranes are clean.

Prostate and Bladder: The sections of these organs are normal.

Gastrointestinal Tract: The mucosa of the bowel is intact but throughout the small and large bowel there is an unusual lymphoid hyperplasia with multiple large masses of hyperplastic germinal follicles in the bowel walls and in the mesenteric lymph nodes (Fig. 10).

Diagnosis

Asphyxia from tracheal compression by an enlarged thymus
Multiple subpleural and subepicardial hemorrhages
Atrophy of the adrenal glands
Lymphatism with status thymico-asthmaticus

CASE 7.—R. L. This baby, an 11-month-2-day-old boy had been taken care of by his aunt and from birth had been weak and not well, although no specific diagnosis had been made of the child's malady. The baby had been under the care of the Stanford-Lane Clinic but had not been seen for the past twenty-four hours. On Aug. 31, 1941, the baby's father, the aunt, and the aunt's husband had had the baby at Edgemar Beach for an outing. At about 3 P.M., while there, the aunt noticed the baby going into a spasm and apparent convulsions which so frightened her that she insisted that the baby be taken to an Emergency Hospital immediately. On arrival at the Alemany Emergency Hospital in San Francisco at 4:22 P.M., the baby was dead. There had been no previous spasms of this type reported and the baby had been born normally after having been carried to term. There had, however, been on occasions episodes of dyspnea.

Autopsy Findings

The child is well nourished and shows a rather marked dependent lividity, but no other pathological changes are evident externally.

The lungs show a normal development but there is a diffuse, patchy atelectasis, some edema, and a moderate congestion throughout the pulmonary parenchyma. The circulatory

and bronchial arrangements are normal at either hilus. The lungs are dissected out in a block with the thymus and heart and the thymus is extremely large, measures 3 by 6 by 2.5 cm. and weighs 35.5 grams. Beneath the capsule of the thymus as well as beneath the pleural surfaces of the lungs there are numerous very tiny petechial hemorrhages. On section of the thymus and lungs these petechial hemorrhages are also found within the parenchyma of both organs. No petechial hemorrhages are found in the heart or beneath the epicardium and the heart is normal in development and shows no congenital anomalies. The foramen ovale and ductus arteriosus are closed.

The liver is normal.

The spleen is moderately congested, a little larger than normal, and sections through it show very large, prominent lymphoid follicles.

The lymphoid tissue elsewhere in the body is normal excepting for rather large nodes at the root of the mesentery.

There are tiny points of opacity which are peculiar and white in color in the wall of the entire gastrointestinal tract, but this is apparently due to dilatation of the lymphatics rather than a lymphatic infiltration.

The adrenals are very small, have thin cortices and practically no medulla. There is no adrenal hemorrhage.

The pancreas, kidneys, bladder, and brain are normal throughout excepting for a little congestion of the vessels of the leptomeninges.

Microscopic Examination.—

Heart: The sections of heart muscle and coronary vessels are normal.

Lungs: Throughout the lungs there is an extraordinary congestion with blood expanding most of the circulatory channels of the alveolar walls and being found loose in the alveolar spaces. About many of the vessels there is a very thin lymphocytic infiltration which is also seen, to some degree, around the bronchioles. There is no consolidation.

Liver: The liver is normal and in the cells there is still a very heavy deposit of glycogen.

Spleen: The spleen shows a hyperplasia of the lymphoid follicles but no more than is normally seen at this age.

Kidneys and Gastrointestinal Tract: The sections are normal.

Sections of the *Nodes in the Mesentery* show a very heavy mass of lymphoid tissue but the follicles show no true hyperplasia.

Thymus: Sections of the thymus show a well-differentiated cortex and medulla with prominent Hassall bodies which are well keratinized and which show no degeneration.

Adrenals: The cortical zones can be clearly differentiated but the glomerular cells are predominant. There is a normal cortical lipoid deposit. The medullary elements are thin but the individual cytology is not abnormal.

Brain: Sections of the brain show no pathological changes.

Diagnosis

Asphyxia following tracheal obstruction by an enlarged thymus
Petechial hemorrhages of the thymus, pleura, and pulmonary parenchyma
Hypoplasia of the adrenal glands
Status thymico-asthmaticus

In this series of twelve cases, seven of which are reported here, there are nine boys and three girls. The only change in gonads observed is the presence of congenital ovarian cysts in one case. These, however, we have often observed in infants dying from causes other than those associated with the endocrine glands or thymus. The ages of the infants run from 7 weeks to 44 weeks, the average age being 21.2 weeks. One stillborn, one adolescent, one adult patient are excluded from these averages. The cases of two infants over 1 year of age dying from tracheal compression and asphyxia with enlargement of the thymus gland, cannot be regarded as pure types of thymic asphyxia inasmuch as one has other endocrine disorders and one is associated with extraneous circumstances (anesthesia) which might induce a cycle ending in asphyxia. In ten of the twelve there is an obvious hypoplasia of the adrenal glands which is evident in both the gross and microscopic studies. That this is not a uniform

circumstance, however, is shown by the two cases in which the adrenal glands are found to be normal. Congenital anomalies, it will be noted, are not a feature in this series, and in all of these cases cited the heart has been within normal functional limits. Furthermore, in the cases where adrenal hypoplasia has been a part of the picture, there has been no hemorrhage within the adrenal cortex or medulla and no pathological changes are observed in the individual cells, the deficit apparently being one purely of volume, although of course, physiological changes cannot be evaluated from the microscopic slides. The presence of a horseshoe kidney in one case is regarded as a miscellaneous finding and not a thing which contributed to the death of the baby. Thymic weights in this series run from 30 to 52 grams, the average being 34.15 grams for the ten cases in which the thymus was weighed. The weight of two of the glands is not recorded because of the desire to save these specimens for museum preservation. The time between the initial attack observed by the mother or nurse and the death of the patients runs from ten minutes to twenty-nine hours. The longer periods elapsing between observation of the baby and finding the baby dead are, we believe, of little significance, but great importance should be attached to the fact that in two of these cases, death ensued within a ten-minute interval between periods of observation. It is our conviction that the attacks in the majority of cases are short and death ensues rapidly and that the longer intervals are simply a matter of circumstance, during which the babies have not been seen. In only two of the cases is there any previous history of respiratory difficulty, and in one of these, a diagnosis of lymphatism, status thymico-lymphaticus, or pulmonary disease was neither made nor suggested. In only one case of this series was a diagnosis of enlarged thymus made before death and, unfortunately in this case, only a recommmendation for x-ray pictures had been made, the baby dying the day he was to have been taken to the hospital for x-ray study. We are fortunate enough to have had one patient, 9 months old, studied before death by bronchoscopy and during these observations the extraordinary posterior curvature of the trachea as it arched behind the thymus gland was observed. In two cases are there evidences of lymphatism other than an enlarged thymus and in these two cases, the peribronchial infiltration of lymphoid tissue demonstrates a perceptible and gradual transition between these pure types of thymic enlargements with asphyxia and the next examples of lymphatism, namely, those cases in which the peribronchial lymphocytic infiltration together with the pathological changes of asthma are paramount in producing the symptoms of bronchial obstruction and in causing death from asphyxia.

Group Two: Status Thymico-Asthmaticus

CASE 1.—R. C. The patient was a 1-year-old, white male who had been born at term by a normal delivery and who had been followed, from birth, by his pediatrician who had observed from that time onward a heart murmur which he attributed to a possible congenital defect. The child also had a cleft palate which extended forward to the gums and an error of fusion on the lip with harelip on the left side. At the age of 3 weeks the harelip was repaired successfully, and at the age of 1 year the patient was admitted to the hospital and prepared for a plastic operation on the palate. The day following entry, ether anesthesia was started at 8 A.M. by the open drop method and changed after induction to nasal tube. At 8:22 A.M., the plastic surgeons started the operation, and at 8:30 A.M., the pulse became irregular and then imperceptible. Artificial respiration was immediately started and continued for forty minutes; oxygen was given by tube; coramine and adrenalin were given by intracardiac injection, but the patient did not revive and death was pronounced at 9:10 A.M. that day.

Excepting for the minor feeding difficulties atendant upon the harelip and cleft palate, the child had been normal in every respect, having had no history of allergy, food dyscrasia, or other difficulty. According to the pediatrician, the only effect of the presumed congenital heart condition was the production of a murmur. There had been no apparent effect upon cardiac function or circulatory efficiency, and the baby was reported not to be typically blue at birth.

Autopsy Findings

External examination shows a chubby, white male, approximately 1 year old, in slight rigor mortis and with a rather marked dependent lividity. The mouth is small, and the harelip has been repaired, showing a very fine scar. The head, eyes, ears, nose, and mouth are normal. The head is rather round in shape; the pupils are equal, symmetrical, and in mid-dilatation. The fontanels are almost completely closed. There is a cleft palate a little to the right in the midline, involving the gums and the soft and hard palate all the way posteriorly with a considerable separation on the posterior end of the cleft.

The skull, upon peeling off the scalp, shows a normal bony structure without deformity or congenital anomalies, and upon lifting off the skull cap, the brain is found to be normal and shows no evidence of injuries, congestion, or edema. Sections through it show a normal structure.

The heart is slightly dilated, but the muscle appears of normal tone. The foramen ovale is open, but the ductus arteriosus is closed. There is a little more dilatation in the right ventricle than in the left, but the heart muscle shows no hypertrophy.

The lungs are deep in color and congested, showing a very slight edema. The congestion is principally limited to the posterior and dependent portions and sections through the hilus on either side show a congestion of all the vascular system, but there is no consolidation and the pleural surfaces are normal.

The liver, spleen, pancreas, adrenal glands, and kidneys are normal. The lymphoid follicles in the spleen are barely visible; the spleen itself weighs only 20 grams.

The gastrointestinal tract is normal, but the mesenteric lymph nodes at the root of the mesentery are extremely hyperplastic and exist as a large mass 4 by 4 by 3 cm. in dimensions. Sections through these show a diffuse hypertrophy of the entire lymphoid structure with some invasion of lymphocytes, which are grossly evident, into the regional fat.

The thymus weighs 32 grams and measures 8 by 5 by 4 cm. One lobe is approximately twice the size of the other, the left being the larger of the two. Sections through the thymus show a normal cortical and medullary differentiation and no gross variations other than those described. The left lobe of the thymus runs almost to the apex of the heart and from this point the lower margin of the thymus then traces a line upward approximately over the point where the septum joins the anterior wall of the left ventricle and thence up to the coronary sulcus where the lower margin of the right lobe travels on around laterally almost in a horizontal direction. Microscopic sections are taken of all the organs.

Microscopic Examination.—

Lungs: Throughout the lungs there is acute congestion and many areas of atelectasis are seen. In the bronchi, many plugs of mucus cause a partial or subtotal occlusion of the airway and about the bronchi and underneath the bronchial mucosa there is a diffuse infiltration of lymphocytes. About and behind the cartilage of the large bronchi the lymphocytes are in very large masses in which there are central hyperplastic germinal zones.

Heart: The myocardium is normal. The coronary vessels are of normal caliber and no pathological changes are seen.

Liver: The sections are normal.

Spleen: The spleen shows a very dense infiltration of the pulp with lymphocytes and with a little increase in the size of the germinal centers of the lymphoid follicles. The follicles themselves, however, are not enlarged. The capsule, trabeculations, and pulp of the spleen are normal. The blood vessels show no pathological change.

Pancreas, Adrenals and Kidneys: Sections of these organs are all normal.

Mesenteric Nodes: Sections show a marked overgrowth of the lymphoid elements with hyperplastic follicles and a plentiful production of lymphocytes throughout and large germinal follicles. Lymphocytes are found growing outside of the margins of the lymph nodes into the peripheral areolar tissue.

Brain: Sections show a marked edema with an exceptional edema of the leptomeninges. In the arachnoid there is an increase in lymphocytic cells, but there is no hemorrhage or degeneration of the brain and the ependymal linings are smooth.

Thymus: Sections show normal cortical and medullary zones with rather immature, poorly keratinized Hassall bodies.

CASE 2.—J. R. G. This 5-year-old girl had been under a doctor's care since birth, having been treated since about 1 year old for asthma. The doctor had not seen the child for about two weeks. She was sleeping normally at 2:15 A.M. on Sept. 9, 1941, at her home, when looked after by her father, but at 7:30 A.M. her mother found her breathless in bed, in a normal position on her back. Her doctor was called and found her dead at 8:15 A.M.

Autopsy Findings

The body is that of a while female about 5 years old. No points of injury are seen. The body has already been embalmed. The head, eyes, ears, nose, and throat are normal.

The heart is very small, weighing 100 grams, and measuring 10 by 6 by 6 cm. The endocardium and pericardium are normal and there are no congenital anomalies. There are occasional subepicardial petechial hemorrhages.

The lungs and the thymus gland are dissected out in a block. The thymus weighs 28 grams and measures 4 by 4 by 7 cm. Sections show very pale but otherwise normal structure. The lungs are aerated, have smooth pleural surfaces, and are apparently normal in development. Sections show no areas of consolidation but the bronchial channels are quite prominent and multiple sections of them are made. The walls show a definite thickening.

The liver and kidneys are normal.

The spleen is very odd in appearance, particularly solid, weighs 100 grams, shows a white, mottled surface, a tense capsule, and sections show peculiar, irregular areas of congestion and anemia.

The adrenals are rather thin but are almost of normal size. Sections show thin cortices and almost absent medulla.

The gastrointestinal tract is normal. The stomach contains some fluid. No lesion is seen in the stomach. The mucosal folds are normal.

Microscopic Examination.—

Lungs: Throughout the lungs there is a partial collapse of the alveolar spaces and in the bronchial and bronchiolar channels there are many mucous plugs. The bronchial mucosa shows some edema and beneath the epithelial layer there is a diffuse infiltration of lymphocytes and plasma cells. There is also an hypertrophy of the bronchial and bronchiolar muscle. Behind the bronchial and bronchiolar walls there are increases of lymphocytes with some of them forming new lymph nodes with hyperplastic centers which push the mucosa into the lumen.

Lymph Nodes: The lymph nodes at the root of either lung show a marked hyperplasia of the follicles in the nodes, which are enlarged.

Liver, Heart and Kidneys: The sections of these organs are within normal microscopic limits.

Spleen: The spleen is extremely anemic but the pulp is normal. The lymph follicles stand out prominently because of the anemia and show a moderate central hyperplasia.

Adrenals: Outside of the adrenal glands which are extremely thin there are small cortical adenomata and the cortex itself shows a poor differentiation with a very thin cortical layer. No medullary cells are seen.

Thymus: The thymus is sharply demarcated into cortical and medullary zones and the Hassall bodies are only fairly developed. There is no degeneration.

Diagnosis

Asphyxia with status thymico-asthmaticus, lymphatism, enlarged thymus and hypoplasia of the adrenal glands.

CASE 3.—R. C. This 7-year-old boy was admitted to St. Francis Hospital on Aug. 5, 1941, at 9:53 A.M. An ether anesthetic by gas induction was begun at 11:30 A.M. ending at 11:55 A.M. During this time an adenoidectomy and tonsillectomy were performed, beginning at 11:40 A.M. and completed at 12 P.M. The patient died at 12:15 P.M., with acute respiratory distress. There was no history taken at the hospital, but the parents make no record of respiratory difficulty or of lymphatism. The tonsils had been enlarged for some time.

Autopsy Findings

The body is that of a boy in his seventh or eighth year. Rigor mortis is slight. There is no evidence of trauma on the body surface. Some bloody material is seen coming from the mouth and upon pressure upon the chest some bloody froth and mucus come from the nose. The heart is normal but on the epicardium, posteriorly, are several subpericardial ecchymotic spots along the course of the right coronary artery. The heart weighs 140 grams and measures 10 by 8 by 5 cm. The endocardium and myocardium are normal. The valves are normal. On the anterior portion of the left ventricle a small patch of hemorrhage is seen in the epicardium measuring about 1 cm. in diameter.

The thymus is enormous and weighs 70 grams; it is one of the largest masses of thymic tissue ever seen in the San Francisco Coroner's Office. The thymus is roughly symmetrical in shape but there is a small third lobe extending down below the main mass which in itself is approximately 3 cm. in diameter.

The pleurae of the lungs are smooth and clean. A small area of bluish discoloration is seen in the posterior aspect of the right lung in the upper lobe. The parenchyma is pale and contains very little air. The bronchi and trachea contain a little bloody material which is now clotted.

The trachea and esophagus are severed just above the larynx and are removed in toto all the way down to the including both lungs. The esophagus is opened and found to be patent with no evidence of occlusion or foreign body. The trachea, upon opening, shows forthy, bloody fluid of a moderate amount, extending all the way down the inner surface to the carina. At the carina and extending into the major bronchi is seen much frothy, bloody material which is quite abundant in amount and which occupies principally all the lumen of these structures.

The enlarged thymus causes a posterior and lateral displacement of the lungs, and the trachea has been thrown into a marked backward curvature as it arches behind the gland.

The liver is normal. The gall bladder is present and normal. The spleen is normal and, on section, has large follicles.

The kidneys are normal, as are the adrenals.

The bladder contains about 50 c.c. of clear urine. The mucosa is intact. The prostate is normal.

The stomach contains some mucous material and dark-colored material of slight amount, plus a moderate amount of gas. The rest of the tract is normal. The appendix is present.

The tonsils are not available for examination.

Microscopic Examination.—

Heart: On one surface of the epicardium there is an area of fresh hemorrhage. The myocardium shows a slight edema. The endocardium is normal.

Lungs: Beneath the pleura in one section is an area of fresh hemorrhage in the alveolar spaces. The lungs show a marked congestion and edema but there is no evidence of inflammation. Sections show mucous plugs in the bronchi in many of the areas sectioned, and behind the bronchial mucosa there is a heavy lymphocytic infiltration. In some areas in the lungs about bronchi and bronchioles, large lymphoid follicles have formed, causing a partial obstruction of the airways. There is a little pulmonary atelectasis with collapse of the alveolar spaces.

Thymus: There is acute congestion throughout the gland. The lobules are large. The Hassall bodies are plentiful and rather mature and the proportional thickness of cortex and medulla is within normal limits.

Sections of the other organs show no pathological changes.

Diagnosis

Bronchial obstruction with acute asphyxia following ether anesthesia
Status thymico-asthmaticus
Operation (tonsillectomy and adenoidectomy)

CASE 4.—J. DeB. This 7-year-old boy had been followed since infancy at the Stanford Clinic, during which time he had developed normally. On Nov. 22, 1934, he was taken into the hospital at 10 A.M. for the removal of enlarged tonsils. Tonsillectomy was done at 12:20 P.M. under ether anesthesia. He was taken from the surgery at 1:05 P.M., came out of the anesthesia slowly during which time there was some cyanosis and died at 4:10 P.M. from acute asphyxia.

Autopsy Findings

External examination shows an excessive amount of hair about the face and abnormally enlarged external genitalia. Both tonsils have been removed from the pharynx and the fossae are free from hemorrhage. The entire respiratory tree is removed and found to be free from obstructions.

The heart measures 8 by 7 by 5 cm. and is of normal size and shape for the age. There are no valvular lesions and the development is normal excepting that the foramen ovale is open and 4 mm. across. The ductus arteriosus is closed.

The lungs are normal and show no evidences of consolidation or infection. There are clots in the vessels at the hilus on either side. The thymus is enlarged and measures 7 by 4 by 2.5 cm. for each lobe. It weighs 35 grams and on section no pathological changes can be seen.

All of the other organs are congested but otherwise normal.

Microscopic Examination.—

Heart: The heart muscle is normal. There are no pathological changes of the endocardium or pericardium.

Lungs: The lungs show considerable congestion and there is some serum in the alveoli. Occasional alveoli are collapsed. Behind the bronchial mucosa, both in the large and small branches, there is a heavy lymphocytic infiltration which usually occurs in nodes but is also diffuse in some areas. The bronchial mucosa is very thick and the bronchial and bronchiolar muscle is hypertrophied. Many lumina contain plugs of mucus.

Liver, Adrenals and Kidneys: Sections of these organs are all normal.

Spleen: There is an unusual hyperplasia of the corpuscles.

Diagnosis

Asphyxia from bronchial obstruction following ether anesthesia
Status thymico-asthmaticus
Operation (tonsillectomy)

CASE 5.—D. S. This patient was a normal girl of 7, who had always been active and well. There had been no serious illnesses. A positive tuberculosis test was obtained two months before death, but x-rays of the lungs were negative and films showed no unusual enlargement of the thymus gland at that time. Two years before death, her tonsils were removed under ether anesthesia, with an uneventful convalescence. The parents had noticed enlargement of the cervical lymph nodes a few days prior to death. On the morning of March 23, 1940, she apparently developed a slight cold and there seemed to be some swelling in the region of the parotid gland, so the doctor was called. He saw her at 5 P.M., at which time she had a temperature of 101° F. There was some dyspnea on inspiration, but the throat was negative to examination. The type of breathing suggested a mild asthmatic attack, but the examination of the lungs showed no wheezing with expiration. She was given 3 minims of adrenalin chloride by hypodermic injection and her respiration became less labored. The physician waited for about twenty minutes, after which time she developed a definite stridor in breathing, but she was not cyanotic at any time. She was then brought to the hospital where she was given oxygen inhalations and 1-100 adrenalin sprays, without improvement. She still did not develop cyanosis, but the difficult breathing continued in spite of these measures. After being in the hospital only about thirty minutes she suddenly threw her head back and breathing stopped.

Autopsy Findings

The body is that of a well-developed and fairly well-nourished, slender child of 7. There is no noticeable cyanosis but there is a moderate lividity of dependent parts. The carotid arteries are carefully isolated, and then the entire larynx and the trachea are dissected out. There is a very slight redness of the mucous membrane of the larynx and trachea, but there is no edema and no exudate on the mucosa. The thyroid is negative except that over the right lobe there is a piece of thymus, the size of a lima bean. The thymus is tremendously enlarged, weighing 40 grams. The lungs are negative except for a moderate congestion in the lower lobes. The bronchi are negative but the peribronchial lymph nodes are enlarged. The heart is normal. The liver is normal. The gastrointestinal tract is normal excepting the Peyer's patches in the ileum which are tremendously enlarged. The mesenteric lymph nodes are also greatly enlarged, some being 2 to 3 cm. in diameter. The lymph nodes along the common bile duct are also 2 to 3 cm. across. The spleen is about 50 per cent larger than

normal and the lymphoid follicles show marked hyperplasia. The adrenals are normal, as are the kidneys. The uterus, tubes, and ovaries are juvenile and within normal gross limits.

Microscopic Examination.—Microscopic sections of the organs are normal excepting those of the thymus, lungs, and lymphatic system.

The thymus shows marked hyperplasia of both cortical and medullary zones, with large Hassall's corpuscles some of which show early calcification. All the lymph nodes, including follicles in the spleen and the follicles of the small intestine show marked hyperplasia with a few eosinophiles present in the stroma of the nodes. The lungs are normal but there are rings of lymphocytes about the smaller bronchioles with some germinal follicles pushing the bronchial mucosa inward. There are plugs of mucus in the bronchi and bronchioles and the bronchial muscle fibers show some hypertrophy.

Diagnosis

Asphyxia with status thymico-lymphaticus and status thymico-asthmaticus

CASE 6.—M. P. This patient, an 8-year-old boy, was seen by his doctor at 8:30 P.M. on Feb. 29, 1940, in the home, for a right lower quadrant pain. This pain was diagnosed as due to an inflammation of the vermiform appendix and the patient was taken to the hospital one hour later where he was prepared for surgery and an appendectomy was done at 10:30 P.M. the same evening. Shortly after midnight that night at 12:50 A.M., he died with inspirational difficulty and some respiratory distress. The appendix removed showed no acute inflammatory process and no evidence of acute inflammatory disease was found elsewhere in the abdomen. According to the history received, the patient took an anesthetic of ether by inhalation without difficulty, the induction stage was easy and there were no untoward effects during the operation. There was no previous history of this boy's life of respiratory difficulty, asthma, recurrent or frequent colds, feeding difficulties, allergy, or other suggestive history.

Autopsy Findings

The child is well developed and nourished and shows no remarkable changes about the surface of the body excepting one small contusion, ¾ inch in diameter, over the left parietal bone. External examination of the body shows a fresh-clipped surgical incision, 3 inches in length, in the right lower quadrant. There is a needle puncture wound in the pericardium where intracardiac adrenalin has been given. The skull is negative and the brain shows a moderate edema with congestion of the surface vessels, and sections through the brain show a normal cortex with symmetrical, undilated ventricles, smooth ependymal linings, and no areas of infection or hemorrhage. The ependymal linings of the fourth ventricle show no granulations. The cerebellum and brain stem are normal. The pituitary gland and pineal gland are normal.

Upon opening the abdominal cavity, the relationships of the abdominal organs are normal.

Upon lifting off the thoracic cage, the lungs seem partially collapsed but lie in clean pleural cavities. Beneath the pleural surfaces there are many fine petechial hemorrhages and the lungs are quite solid. Sections through them show a few spotty areas of increased density of deep red color suggesting an irregular atelectasis. No exudate is found in the bronchioles grossly and there is no visible change in the lymphoid elements in the hilar nodes. Examination of the trachea, larynx, and bronchi shows a small amount of seromucinous material tinged with a very little blood in the upper respiratory tree, and in the fibrous tissue around the trachea, as well as underneath the capsule of the thymus, a few fine petechial hemorrhages are found.

The heart weighs 160 grams, measures 12 by 9 by 5 cm., and is markedly dilated. There are no congenital anomalies. The heart is not hypertrophied. The coronary system is patent and sections through the heart show a normal muscle and valves. The auricles are compressed.

The thymus is extremely large, weighs 34 grams, and measures 8 by 6 by 3 cm. Sections through it show symmetrical lobes with a good line of demarcation between cortex and medulla. There are no gross pathological changes.

The lymphoid follicles of the spleen are very large, measuring a millimeter in diameter each. They are closely packed in the spleen and the splenic pulp is congested with erythrocytes. The capsule, trabeculations, and pulp, however, appear grossly normal.

The liver, gall bladder, pancreas, kidneys, bladder, prostate, and gastrointestinal tract are normal. The stomach contents, blood, and sections of liver and kidneys are submitted for toxicological examination with negative results.

Microscopic Examination.—

Lungs: Sections show a diffuse congestion with collapse of many of the alveolar spaces. In the alveolar spaces there is occasionally a little serum but there is no consolidation either with erythrocytes or pus. The bronchioles are frequently collapsed and about the bronchioles are large nests of lymphocytes which are occasionally held in follicles with hyperplastic centers. These are found running well out into the terminal bronchioles and the lymphocytic infiltration is particularly dense about the primary tubes. There is also a marked edema of the bronchial mucosa and a little hypertrophy of the bronchial musculature, and there is some increase in fibrous tissue behind some of the larger bronchioles directly beneath the basement of the mucosa. A little mucus is seen in the bronchial and bronchiolar channels.

Thymus: Sections show normal cortical and medullary zones, the cortex being quite thin, the majority of increase in size being in the medulla. The Hassall bodies are very well differentiated and mature.

Heart: The heart muscle shows a moderate edema but there is no fibrosis or degeneration. The coronary system is patent. Beneath the pericardium as well as beneath the pleura are many fine aggregations of erythrocytes.

Spleen: Section shows normal trabeculations and pulp and there are many erythrocytes held in the pulp with an increase in the erythrocytic relationship. The lymphoid follicles are very large and nearly all the centers are hyperplastic.

Liver, Kidneys, Pancreas, Adrenals, Gastrointestinal Tract, Brain, and Pituitary Gland: Sections of these organs are all normal.

Pineal Gland: The gland is small and measures 2 mm. diameter, but the cells appear normal.

Diagnosis

Asphyxia from bronchial obstruction with pulmonary atelectasis, status thymico-asthmaticus

Status thymico-lymphaticus

Operation (appendectomy)

CASE 7.—S. L. This 13-year-old Chinese boy and his 19-year-old sister arrived from China on Sept. 6, 1941, en route to their father's home in Arkansas. On Sept. 9, 1941, while he was a guest at a hotel, he fainted. A doctor was summoned who made a diagnosis of acute appendicitis. The child was admitted to the Chinese Hospital at 10:36 A.M. and at 5:50 P.M. an appendicectomy was done. Near the conclusion of the operation the patient's blood pressure dropped, respirations ceased, and death was pronounced at 6:30 P.M. on Sept. 9, 1941. The anesthetic administered was nitrous oxide gas induction followed by ether inhalation.

Autopsy Findings

The subject is a Chinese boy in his early teens. Rigor mortis is present. The body surface is negative for evidence of trauma. The right lower quadrant shows a recently performed right appendicectomy scar, 2⅛ inches long, and still has skin clips in place.

All of the organs have an extraordinarily heavy smell of ether.

The brain weighs 1,500 grams, is very large for this age, and measures 20 by 15 by 10 cm. It shows some edema but the hemispheres are symmetrical, and there is no bleeding in the leptomeninges. Sections show symmetrical, undilated ventricles and smooth ependymal linings. There are no changes in the cerebellum or stem. The pituitary and pineal glands are normal.

The heart weighs 190 grams and measures 12 by 9 by 6 cm.; it is normal and there are no congenital anomalies.

The thymus gland is removed in a block dissection together with the esophagus and trachea. The esophagus is normal, the aorta shows no pathological changes, and the trachea to its bifurcation and including some of the bronchus on either side is normal. The thymus weighs 36 grams, measures 8 by 6 by 2.5 cm. The lobes are asymmetrical, the right one being 5.5 cm. long, and the left 8 cm. The capsule is normal and sections show a little central degeneration and liquefaction with normal lobular markings.

The lungs are rather boggy and wet and show a moderate edema. The pleural surfaces are smooth. Sections show areas of edema with a little hemorrhage in the dependent portions. The bronchial channels and the roots of the lungs appear grossly normal. There is no bronchial obstruction.

The liver is normal in color and appearance although rather pale, and sections show normal lobular markings.

The splenic capsule is stretched rather tightly and there are some adhesions on the outer surface of the spleen. Section shows only congestion in the pulp with visible lymphoid follicles.

The pancreas and adrenal glands show no gross pathological changes.

The stomach contains only mucous material and fluid. The rest of the gastrointestinal tract is negative, except for the presence, in the region of the right lumbar gutter, of a few catgut sutures and some freeing of the cecum in this region. At the end of the cecum in the region of the appendix, there is seen evidence of recent surgical procedure with apparently removal of the appendix.

Microscopic Examination.—

Lungs: The lungs are extraordinarily edematous and in some of the alveolar spaces there are pigment-laden phagocytes. Other alveolar spaces are filled with erythrocytes mixed with serum and fibrin. There is, however, no purulent consolidation. Sections of the bronchi show channels completely occluded with mucous plugs and behind the bronchial mucosa which is rather heavily folded there are marked infiltrations of lymphocytes and eosinophiles. There is also an increase in the thickness of the bronchial musculature. This development does not extend for any appreciable distance out into the lesser bronchioles but is marked at either hilus. Many alveoli show complete collapse.

Liver: The liver shows a little cloudy swelling of the cytoplasm of the cells and there is a definite increase in lymphocytes about the portal spaces for this age.

Spleen: The spleen shows an intense congestion with both serum and erythrocytes but the corpuscles are not overactive and the pulp is normal.

Heart, Thymus, Pancreas, Kidneys, and Adrenals: Sections of these organs are within normal microscopic limits.

Brain: The section shows an intense edema and congestion but no other pathological changes.

Diagnosis

Asphyxia following bronchial obstruction
Status thymico-asthmaticus
Operation (appendectomy)

These seven cases are reported as a representative group, which in the aggregate closely resemble a far larger group which space forbids including.

Six of these seven, it will be noted, have been given an anesthetic at varying intervals before the terminal asphyxia, thus supplying the trigger mechanism necessary for the precipitation of an acute attack of asphyxia with strangulation in these cases. The duration of the attack of partial asphyxia preceding death varies from forty minutes to thirty hours. This interval is of some interest inasmuch as it is appreciably longer than the observed interval in cases of apparently spontaneous asphyxia where no anesthetic has been used.

In the group are two female, and five male. The ages vary from 1 to 13 years. The average of this group, 6.8 years, is somewhat higher than in the preceding group of deaths from asphyxia with an enlarged thymus, but with no cytological changes similar to those seen in asthma. All of the seven were found at autopsy to have large thymus glands, the average weight being 37.7 grams. In only one of this group, however, was an enlarged thymus suspected before death.

In one 12-month-old baby, dying one hour and ten minutes after induction of an anesthetic given for an operation closing a harelip, there is a congenital anomaly, the patent foramen ovale. This, however, was regarded by the pediatrician attending the child as causing only a functional murmur.

In only two of the seven children is there a previous history of asthma elicited in conversation with the parents, but all of these cases have common

microscopic changes in and about the bronchi, which typify asthma in older people and which, in connection with the enlarged thymus observed, lead us to include them together in the status thymico-asthmaticus group. While found occasionally in these cases, hypoplasia of the adrenal glands is observed in only one of the seven and is far less common in this classification than in those children dying from obstruction by an enlarged thymus alone.

It is probably noteworthy that in instances here where adrenalin was used, the usual beneficial effect of bronchial relaxation was not observed. This, in part, may be due to the marked cytological changes which exist in and about the bronchi and bronchioles and in part possibly due to the unusual degree of mucous secretion observed at autopsy.

The bronchial, bronchiolar, and adjacent pulmonary changes observed in this group are not necessarily associated with an enlarged thymus and we have on record instances of strangulation and asphyxia following occlusion of the airways by this same pathological mechanism where the thymus has not been enlarged. There is no direct evidence pathologically or studies clinically which enable one either to rule in or eliminate allergy in these cases. There is a fair history of allergy elicited occasionally but we have observed identical pathological changes as described here repeatedly in infants and young children who have had no history of allergy and have in fact seen these changes in stillborn infants. On the negative side, similar bronchial, bronchiolar, and peripheral pathological changes of this type have been not infrequently seen in children dying from other causes, either diseases or accidents, who have never had any respiratory difficulty. We also have on record deaths during and following anesthesia, where these changes were not found, but in these cases acute pulmonary atelectasis, aspiration of foreign material, particularly blood, or improper administration of the anesthetic explained the death. After all these are screened out then, there still remains the residue of children who have a lymphatic constitution and enlarged thymus, or a normal gland, normal or hypoplastic adrenals, plus specific bronchial, bronchiolar, peribronchial, and peribronchiolar changes which may be either latent or incipient, but which remain in the background as potential dangers and which occasionally in our experience are responsible for asphyxia. These changes have been observed from birth to the age of 13 years, covering the entire period of infancy and childhood.

Group Four: Hyperinvolution of the Thymus Gland

THYMIC LYMPH TOXINS, ACUTE TOXIC INVOLUTION OF THE THYMUS, ACUTE DEGENERATION OF THE HASSALL BODIES, AND RELATED STATES

Death from a toxic material thrown into the systemic circulation by the thymus gland has been a presumption by some and, as previously reported, Svelha[43] found an extract of thymus to be lethal, in experimental animals, particularly when it contained large amounts of nonspecific protein material. More or less paralleling this experimental experience, we have, in company with other investigators, often observed sudden death, particularly in infants and young children, where in addition to minor or major systemic diseases of many sorts, there has been a medullary degeneration of the thymus gland with a partial liquefaction, a brown discoloration and, by microscopic study, specific changes in the Hassall bodies. The observation of these changes leads to a perhaps erroneous conclusion that the degenerative phenomena observed in

the thymic medulla are responsible for death and not a part of the systemic disease which may exist in conjunction.

We have on record cases of acute involution of the thymus gland with degeneration of the Hassall bodies where there is no intercurrent disease or absorption of toxin, previous x-ray therapy, electric shock, hemorrhage, or other background of disease, physical or chemical change, to which this involution could be attributed. On the other hand, acute involution of the thymus including both cortex and medulla is so common in infectious diseases as to be almost a rule in our experience and it occurs rapidly. A marked reduction in size of the thymus gland may occur in a period of only forty-eight to seventy-two hours and during this period of shrinkage, the changes in the Hassall bodies begin in the center, the normal keratin material (Fig. 7) undergoing some liquefaction, granular degeneration, and appears as a very fine, granular, pink and precipitated protein debris within the capsule of the Hassall body. Shortly after this time there is an infiltration of leucocytes, many of which are eosinophilic polymorphonuclear cells together with some lymphocytes (Fig. 8). Later, there appears a granular, blue debris which, to our present knowledge, is an unknown substance, and following these changes, the capsules or walls of the Hassall bodies may break entirely (Fig. 9). There is then a dispersion of this material in the medulla of the gland. These acute involutional changes we believe to be subsequent to and a sequence of disease rather than the cause of disease, but the liberation of such material may in itself provoke a systemic reaction. We have seen this involution occur following x-ray treatment of the thymus gland, after the exanthemata, diphtheria, pneumonia, tetanus, pertussis, following surgical shock, electric shock, and associated with acute adrenal hemorrhage during and after exposure to cold and in death from massive surface burns of the body. The rapidity of involution of the gland in cases with toxic systemic disease explains in a large degree the wide variation of the thymic weights cited in the literature and we have numerous cases on record, both at the San Francisco Coroner's Office and the San Francisco City and County Hospital where following not more than a week of toxicity from disease the thymus gland will be found at autopsy to weigh not more than 4 grams.

In reporting case examples of hyperinvolution of the thymus, all the cases on record in our files will not be produced, but specific case types only are recorded in an effort to save space. These cases can roughly be divided into four groups: those suffering from physical effects such as burns, shock, x-ray therapy and freezing; involutions following virus or bacterial diseases; malnutrition and idiopathic hyperinvolution. In all of our instances excepting one, it is, of course, not possible to evaluate accurately the weight of the thymus before involution began, and it can, in criticism, be fairly said that one does not know whether or not the thymus has actually been reduced in size. Taking as the base line, however, the normal thymic weight of the individual, as determined in this particular district by our own criteria, it can be said that the thymus in each of these cases is distinctly smaller than the average.

Further criteria are the relative gross decrease in size of the medulla and the microscopic changes in the Hassall bodies as described above. In one of these cases we have, fortunately, x-ray pictures of the thymus gland, proving by shadows that it was, before x-ray therapy, enlarged. Whether it was larger at this time than it was found to be at autopsy is again an unprovable point, but the same criteria apply here as in other cases. It is worthy of note

in this case (E. B. G.), which is the third to be subsequently presented, that this baby's brother, 4 years his senior, was regarded by his pediatrician as a case of status thymico-lymphaticus, received x-ray therapy during the first year of life, and suffered several episodes of partial asphyxia, from which he was resuscitated with great difficulty. This child, at present, is 4½ years old and for the past two years has shown no symptoms of lymphatism.

CASE 1 (Malnutrition and Dehydration*).—K. W. This baby, a 2-month-old boy, had been delivered normally after a full-term pregnancy. Being an illegitimate child, he was relinquished to a local bureau for adoption, and was placed by them with a family on Sept. 8, 1943. On the first of October, the baby was brought to Mission Emergency Hospital in San Francisco by an unknown person, on the orders of a local doctor, because of dehydration and malnutrition. The child died the following morning at 5:55 A.M. apparently from these causes.

Necropsy

External examination shows a male infant approximately 2 months of age and quite dehydrated. The fontanels are sunken and the nutrition is poor. The body is quite cold, but there is no rigor mortis. There are no surface evidences of trauma.

Upon opening the body, very little subcutaneous or intra-abdominal fat is found, but the organs are in the normal relationship and show no congenital anomalies. The organs are all rather small and pale, but no pathological changes or variations from normal are found excepting in the brain, adrenals, and thymus gland.

The brain shows only a moderate edema.

The adrenals are slightly larger than the normal glands at this age and sections through them show cortices running approximately 1 mm. through its thickness on either side with a definite increase in medullary elements which are very dense and white.

The thymus gland is very small, weighs approximately 12 grams, is roughly symmetrical, and sections through it show well-demarcated cortical and medullary zones with no medullary degeneration.

Microscopic Examination.—

Brain: Sections show only a little edema, but are otherwise normal.

Adrenals: The cortical zone of the adrenal gland shows a depletion in lipoid constituents in the fascicular areas, and there is a relative increase in medullary cells. There is no medullary hemorrhage, or adenomatous formation.

Thymus: There is a marked atrophy of both cortical and medullary zones and the number of cortical cells appears diminished. Medullary cells are also reduced in number and there is a diffuse degeneration of the Hassall bodies, with a peculiar degeneration throughout the keratohyaline centers of these bodies, which are now rather soft, granular material, staining with eosin and throughout which are infiltrations of eosinophiles, and a few polynuclear cells together with a thin scattering of lymphocytes.

CASE 2 (Malnutrition and Congenital Heart).—N. J. B. This 17-day-old baby girl had been born at term by a normal delivery and had been kept in the hospital twelve days. During the ensuing week, the parents had considerable difficulty feeding the baby, because of her lack of vigor and inability to nurse. On Oct 7, 1943, seventeen days after birth, the baby's father was taking her, by streetcar, to the U. C. Hospital for a checkup in the well-baby clinic, when he noticed her beginning to breathe very heavily. She regurgitated food through the nose and mouth and approximately fifteen minutes later, when her father arrived at the hospital with her, she was dead.

Necropsy

External examination shows a well-developed, but poorly-nourished white baby girl, still warm, and showing no external marks of significance. The skin and subcutaneous tissue are well hydrated, but the subcutaneous fat is thin. No congenital anomalies or pathological changes are found excepting in the heart, lungs, and thymus gland.

The heart is of a peculiar, globular shape, shows a massive dilatation and measures 6 by 5 by 4 cm. Beneath the epicardium there are numerous fine petechial hemorrhages, and upon opening the heart, an odd anomalous development is seen at the top of the interventricular septum, where there is a hiatus approximately 2 cm. in diameter, across the

*Complete autopsy studies were done on all of these cases, but only the essential findings are given here.

inferior margin of which lies a rather large blood clot with one end lying underneath the medial aortic cusp. The valves are normal, but the conus is dilated, and there is a hypertrophy of the right ventricular muscle, it being almost exactly as thick as the muscle on the left side. There is a fibrous band running from the anterior papillary muscle just below the attachment of the chordae tendineae, to the left lateral ventricular wall on an almost horizontal plane. Foramen ovale and ductus arteriosus are opened and just past the orifice of the ductus arteriosus there is a moderate coarctation of the aorta.

Both lungs are atelectatic and there are numerous subpleural hemorrhages. No foreign material is found within the lungs, but in the trachea and many of the major bronchi are numerous small, yellowish-white flecks, which are similar to the material seen in the stomach, and has apparently been freshly aspirated.

The thymus is very small, weighs only 8 grams and measures 5 by 3 by 1.5 cm. The lobules are roughly symmetrical and the thymus, on section, is very pale. The cortex and medulla are poorly differentiated, and there are fine petechial hemorrhages throughout the gland.

Microscopic Examination.—

Heart: Sections show no microscopic anomalies of the coronary arterial structure, but the muscle sections show a loss of striation in many of the fibrils, and in places the sarcolemma is filled with very fine fibrous tissue, which is edematous, instead of muscle. There is no cellular infiltration.

Lungs: Throughout there are many congested vascular channels within the alveolar walls and most of the alveolar spaces are collapsed. The bronchi and bronchioles, however, are open and there is no consolidation within the alveoli or debris now seen within the bronchial lumina. Fine petechial hemorrhages are seen beneath both pleura and pericardium.

Thymus: The cortex and medulla are both greatly reduced in thickness, and there are fine petechial hemorrhages, particularly within the cortical zone. The Hassall bodies are extremely small, many are degenerating and within the capsules of the Hassall bodies is amorphous protein debris, and within these areas of debris and degeneration, there are leucocytes and many eosinophiles.

CASE 3 (X-ray).—E. B. G. This 2-month-old baby boy was born by cesarean section after a full-term pregnancy. At birth there was a small, fibro-epithelial polyp on the anterior surface of the neck, on the right side, and there was a right-sided harelip, and a cleft palate. The baby ate well, gained normally, and early repair of the lip and palate was decided upon. Before attempting surgery, an x-ray was taken of the baby's chest to evaluate the size of the thymus gland, and it was found to be definitely enlarged by x-ray. One week before death, the baby was taken to the x-ray department at a local hospital, a therapeutic exposure of the thymus region was made, and the baby was taken home with no untoward effects. One week later, on June 19, 1943, the baby was taken to the same hospital for a second x-ray treatment, which was given at 12:30 P.M. He was then taken home and placed in his crib, face down. At 2 P.M. his mother went to the crib to give him his 2 o'clock feeding and found him dead. There were no pillows in the crib and there were no clothes over the baby's head, or other obstructions of the airway at the time.

Necropsy

External examination shows a well-developed and fairly well-nourished white male infant. There is a right-sided harelip, a cleft palate, and there is a small, soft fibroma on the right side of the neck approximately over the sternocleidomastoid muscle. External examination is otherwise negative.

The skin and subcutaneous tissue apparently are normal. There are no gross congenital anomalies, and the organs are normal excepting the heart, lungs, thymus, and adrenal gland.

The heart is normal in size, shape, and position. There are frequent fine petechial hemorrhages within the myocardium and beneath the epicardium. The foramen ovale is patent. The ductus arteriosus is closed.

The lungs show marked atelectasis and weigh 60 and 45 grams for the right and left, respectively. There are numerous petechial hemorrhages beneath the pleura, and there are hemorrhages within the pulmonary parenchyma on the right side. The major bronchi and bronchioles, however, contain no debris or mucus.

The thymus is within normal gross limits, weighs 20 grams and is symmetrical. Cut sections through it show no areas of hemorrhage or degeneration.

The adrenals show extremely thin cortices, separated by only a few medullary cells, and there is a marked congestion of the vascular channels within the medullary areas. The cortical cells are extremely pale.

Microscopic Examination.—

Heart: Sections of the myocardium show no pathological changes.

Lungs: Throughout there is a moderate atelectasis with many alveolar spaces collapsed. There are fine hemorrhages beneath the pleura and in the pulmonary parenchyma. There is, however, no hypertrophy of the bronchial musculature and there is no peribronchial or bronchiolar lymphocytic infiltration. The bronchi and bronchioles are empty.

Adrenal: The cortices are thin. The medullary cells are relatively reduced in number and outside of the adrenal capsules there are numerous very small adenomas made up of glomerular cells.

Thymus: Both cortex and medulla are reduced in thickness, but there are no hemorrhages. In the medulla the Hassall bodies show a diffuse central degeneration with eosinophilic and leucocytic infiltration within the capsules of the bodies (Fig. 10).

CASE 4 (Second Degree Burns and Pneumonia).—N. S. This 6-month-old baby girl was a normal full-term delivery, and while at home with her parents on July 20, 1943, became ill. A local doctor was called the following day who treated her for a cold and from the twenty-first to the twenty-eighth of that month she gave the baby's parents instructions by telephone for treatment. On July 28, 1943, while the baby's father was holding the child and preparing hot water on the stove for inhalation, the container of hot water tipped from the stove and came into contact with the baby's left leg causing second-degree burns. The baby was taken immediately to a local hospital, admitted at 2:30 A.M. July 28, 1943, treated for second-degree burns of the leg and lobar pneumonia. The child died that morning at 7:25 A.M.

Necropsy

External examination shows a very well-developed, well-nourished female infant. There are second-degree burns on the left lower extremity involving the entire posterior medial aspect of the thigh and leg, and there is a second-degree burn on the dorsum of the left foot with blisters filled with clear, serous fluid seen here and also just below the groin on the left. There are also two small burns on the dorsal aspect of the right foot.

The initial incision is through a normal layer of subcutaneous fat. The peritoneal cavity is normal, and the organs are within normal gross limits.

Upon lifting off the thoracic cage, no free fluid is found, but there is a complete consolidation of the left lower lobe. This consolidation is in the red stage, but among large fields of red parenchyma, there are occasional small, pale patches. There is no pus in the bronchi, and the other four pulmonary lobes are normal excepting for a few small areas of atelectasis in the left base.

The thymus is rather small, weighs 9 grams and measures 2.5 by 3 by 3.5 cm. The lobes are symmetrical and sections through the thymus show no gross pathological changes.

The adrenals are normal in size and weigh approximately 2.5 to 3 grams apiece. Sections through them show well-developed cortices and medullary areas.

The brain shows a little congestion with numerous areas of intervascular clotting in the surface vessels. Sections through the brain, however, show no pathological changes.

Microscopic Examination.—

Heart: The heart is normal.

Lungs: Through the lungs there is an acute purulent infiltration throughout the alveolar spaces which are adjacent to the bronchi and bronchioles, and this consolidation is spreading out peripherally in the lobules to become confluent. There is also a marked edema and a congestion of the circulatory channels in the alveolar walls.

Liver: The sinusoids of the liver contain no erythrocytes and there is occasionally a little cloudy swelling of the Kupffer cells, as well as the cytoplasm of the liver cells proper. The portal veins and bile ducts are normal.

Kidneys: The kidneys are normal.

Spleen: The spleen shows a relative anemia but is otherwise normal.

Pancreas: The pancreas is normal.

Adrenals: Cortices show a depletion of lipoid in the fascicular areas, but there are no other changes. Within the medullary zones, medullary cells are very thinly scattered and between them there are a few free erythrocytes in the fibrous stroma.

Brain: The brain shows a diffuse congestion with a little edema of the leptomeninges, but there are no other pathological changes.

Thymus: The cortical zones are thin, but there is no hemorrhage or degeneration within the cortices. The medullary cells are reduced in number and the Hassall bodies are swollen.

The keratinization is incomplete and there are granular masses of debris within the capsules of the Hassall bodies which are occasionally dilated. Some of this material is deeply basophilic in staining reaction and most of it appears amorphous and without structure. There are no hemorrhages within the medulla.

CASE 5 (Tracheobronchial Tuberculosis, Bronchopneumonia, Diarrhea, Dehydration, Malnutrition).—F. B. This 8-month-old baby girl was en route to Ukiah with her parents when she became ill with nausea, diarrhea, and fever. Upon arrival at Ukiah, she was taken to a local doctor, who examined her and treated her for a cold. Two days later on August 26, 1943, the family returned to San Francisco, but the baby still appeared ill. On August 30, she was taken to a local hospital where she was examined and hospitalized at 6:45 P.M. A diagnosis at this time was made of an upper respiratory infection and diarrhea, but the baby died before treatment could be instituted at 11:30 P.M. the same day.

Necropsy

External examination shows a rather small female infant, showing evidence of dehydration, weight loss, and malnutrition. There is no surface evidence of trauma. The skin and subcutaneous tissue are dehydrated. There is a rather thin layer of subcutaneous fat, but the abdominal cavity is clean, and the organs are normal.

Upon lifting off the thoracic cage the lungs show only a fair aeration and on the right side in the right lower lobe there is a small, localized abscess, which is directly under the interlobar septum and around it are several small white satellite areas. Elsewhere throughout the pulmonary parenchyma there are tiny white nodules with rather firm, but caseous centers, similar to the larger mass. These run from 0.5 to 1.5 mm. in diameter. There is no consolidation of the pulmonary parenchyma between these. At the bifurcation of the trachea there is a large white mass approximately 3.5 cm. in diameter which envelops the trachea and bronchi at this point. Throughout the mass there is a heavy central caseation with a peripheral wall of fibrous tissue.

The thymus is extremely small, weighs 7.5 grams and measures 5 by 3 by 0.7 cm. It is very white in color, rather soft, and sections through it show an involution and a marked reduction in the size of both cortex and medulla, and throughout both zones there are tiny fine areas of petechial hemorrhage.

Microscopic Examination.—

Lungs: Throughout the pulmonary parenchyma there is a most acute tuberculosis with many areas of coagulation necrosis replacing pulmonary parenchyma. Around these areas there are peripheral giant cells, some young fibrous tissue, and a diffuse lymphocytic infiltration. In addition to these, elsewhere in the pulmonary parenchyma there are many young endothelioid cells in aggregations, as yet not undergoing a central caseation. Sections through the tracheobronchial nodes show a much older lesion and apparently the primary one in this case with a rather heavy hyaline fibrous capsule around large central cords of coagulated protein, which has entirely lost its structure. There are no lymphoid elements here now and only rare peripheral giant cells are seen while there are lymphocytes scattered throughout the hyaline fibrous capsule.

Thymus: The thymus shows a diffuse involution of both cortex and medulla with a marked reduction in the thickness of the cortex and in the volume of cells. There is no degeneration here. In the medulla, however, there are fine areas of hemorrhage throughout the medullary areas and the Hassall bodies are degenerating, are small, have very heavy fibrous capsules within which there is a granular debris now without structure excepting for occasional polymorphonuclear leucocytes which are seen mixed with the granular material.

CASE 6 (Bronchial Asthma, Bronchopenumonia).—D. F. This 18-month-old baby girl started vomiting and having diarrhea approximately 4 A.M. on Oct. 19, 1943. Her parents gave her castor oil which she retained and ceased vomiting for approximately twelve hours while the diarrhea continued. At 4 P.M. that day she began to vomit again and was taken to the Central Emergency Hospital where a diagnosis was made of bronchopneumonia and malnutrition. She was transferred immediately to the San Francisco Hospital, but was dead on arrival at 5:27 P.M., the child at that time having a temperature of 108° F.

Necropsy

This baby is a well-developed, rather poorly nourished Mexican infant showing no external findings of importance excepting some beading along the costochondral junction.

The initial incision is through a very poor layer of skin and subcutaneous fat. The abdominal relationships are normal. Upon lifting off the thoracic cage numerous tiny petechial hemorrhages are seen in the epicardium, but the heart is otherwise normal.

Both lungs show a moderate atelectasis which is spotty and around these areas there is a little apparent early consolidation. Mucopurulent material can be expressed from the major bronchi.

The adrenals are extremely small and hypoplastic, the cortices running less than 1 mm. across in thickness and there is no medullary substance visible grossly. There is, however, no hemorrhage.

The thymus is rather small, weighing 20 grams, and the hemispheres are nearly symmetrical measuring 3 by 5 by 2 cm. each. Sections through the thymus show well-developed cortical and medullary zones and very tiny petechial hemorrhages throughout the gland. The capsule is normal.

All of the other organs are normal to gross examination.

Microscopic Examination.—

Lungs: Throughout the lungs there is a diffuse atelectasis and the bronchial and bronchiolar channels contain a mucopurulent debris. The alveolar spaces near the bronchial tree are occasionally partly filled with pus. The bronchial and bronchiolar lumina are small, flattened, and compressed due to a very heavy lymphocytic proliferation which frequently lies in large nodules just outside the bronchial and bronchiolar walls. These lymphocytic aggregations are especially dense around the larger bronchi, but extend even to the terminal radicals. A few adjacent alveolar spaces contain pus.

Thymus: Shows a marked reduction in thickness of the cortex, with a diffuse granular and amorphous degeneration of the Hassall bodies.

Adrenals: Show very thin cortical and medullary zones, but outside of the capsule there is no hemorrhage.

Of the six cases reported in this group, two had congenital anomalies, one a congenital heart with a patent foramen ovale, ductus arteriosus and the second with a harelip.

The average age of the two boys and four girls is a little over 6 months. All of these with the exception of the last case, died of primary disease condition unassociated with the thymus gland or the lymphatic system, and all six of them show the hyperinvolution of the thymus consistently seen in children in a poor state of nutrition. Further evidences of the low nutritional level are the absence of rigor mortis in Case 1 and the depletion of the cortical lipoid and the reduction in size of the adrenals generally of the whole group, a condition quite contrary to the usual findings of relatively large adrenal glands, where there is a normal or small thymus unaffected by disease.

Case 6, with death from asthma and bronchopneumonia was a status thymico-asthmaticus, but the acute pathological changes now so overshadow previous existing conditions, that this death cannot be entirely attributed to this condition.

Group Five: Familial and Hereditary Factors

STUDIES OF FAMILIAL AND HEREDITARY INFLUENCES

Odd, and deeply interesting, is the first report of Status Thymical Lymphaticus made in medical records, because it is also the first reference in medical literature to the familial structure of this condition. It was, in fact, the familial and tragic sequence of death in the sons of Marcus Peresius that led him to request his family physician to do an autopsy upon his 5-month-old son.

According to Ruhräh's *Pediatrics of the Past,* Plater (1614) reports this case, who was a 5-month-old, well-nourished baby boy with no previous illnesses, who died suddenly from difficult breathing and suffocation. As the father had already lost two sons from the same malady and was desirous of knowing the cause, he requested an autopsy and the chest of the baby was opened at his re-

quest. A large gland was found in the region of the throat which had assumed the proportions of a tumor, was "one ounce in weight, spongy, fleshy and pendant, replete with veins, adherent by membranes to the largest descending vessels adjacent to the throat, and congested. The large vessels of the throat were filled with blood and were flowing into the struma." The gland itself appeared of sufficient size to compress the blood vessels in the locality, and it was by this mechanism, together with the size of this mass over the trachea, that Plater concluded the child was suffocated. Since Plater's time, little has been made of the family association of an enlarged thymus gland in siblings, and while such cases are not numerous in our series, they do occur.

In the three pairs subsequently reported, the diagnosis of an enlarged thymus was made clinically and by x-ray in the first pair and after treatment both children lived. In the second pair a diagnosis of enlarged thymus was made by x-ray and by clinical examination, and subsequent to x-ray treatment one of the pair lived while the other died after the second exposure to therapeutic short rays. In the third pair, which were twins, both of the infants died suddenly from suffocation at almost the same time and a diagnosis of an enlarged thymus gland with suffocation was made at autopsy.

CASE 1.—E. B. G. and H. G. The elder of these two brothers (H. G.) had been a normal, full-term delivery and presented during the early months of his life no feeding or nutritional problems. At approximately 5 months of age, the baby began to have recurring episodes of dyspnea and cyanosis, together with some respiratory stridor. Tracheal pressure from an enlarged thymus gland was suspected and skiagrams showed both an enlarged thymus gland and tracheal compression with posterior displacement. A course of x-ray therapy was started and during this time the attacks of partial asphyxia continued from which the child was resuscitated with great difficulty. At approximately 12 months of age and after the completion of the x-ray therapy, these attacks gradually diminished in intensity and finally ceased entirely. This child is at present 4½ years old and for the past two years has shown no signs of lymphatism and there have been no evidences of dyspnea, tracheal obstruction, or other signs and symptoms contributable to an enlarged thymus gland. By x-ray now the gland appears normal, and there have not developed to date any symptoms which might be attributed to a developing allergy.

E. B. G., reported as Case 3 of hyperinvolution of the thymus gland, was a 2-month-old baby boy born by cesarean section and, as previously reported, at the age of 2 months was to be operated upon for a harelip and cleft palate. Because of the family history and a little respiratory distress at times, an x-ray was taken of this baby's chest before any surgery was attempted and the thymus was found to be enlarged. X-ray therapy was decided upon, it being felt advisable to shrink the thymus down to normal size before doing the necessary surgery. The baby had received one x-ray exposure therapeutically and one week later a second similar treatment was given at 12:30 P.M. He was then taken home and placed in his crib face down. At 2 P.M. his mother went to the crib to give him his 2 o'clock feeding and found him dead.

Necropsy showed the thymus at this time to be within normal limits, weighing 20 grams.

Microscopic studies, however, showed a hyperinvolution of the gland with characteristic changes in the Hassall bodies.

CASE 2.—This pair of 11-month-old twin boys were normal full-term deliveries excepting for the twin birth and subsequent to their delivery, they had been normal, had presented no feeding or nutritional problems, and there had been no other evidences of disease. No stridor, dyspnea, or cyanosis had been noted either by the mother or the attending physician. They were fed at the usual hour and at the same time one evening, placed in separate beds, on similar mattresses covered with similar covers and apparently went to sleep at approximately the same time. There were no mechanical body controls used and no pillows were in the cribs. At approximately 11 o'clock that night the family returned from the theater and on entering the children's room to see if they were properly covered, found them both very still and apparently not breathing. The family physician was called, who pronounced them both dead.

*Necropsy**

Autopsies done by the autopsy surgeon for the Coroner's Office showed normally developed and nourished 11-month-old baby boys, free of congenital anomalies. No pathological changes were found during the necropsy studies, excepting very large thymus glands, which were approximately the same size and which caused posterior tracheal compression, upon the great veins and vessels of the neck, and anterior rotation of the bases of the lungs. Petechial hemorrhages of asphyxia were observed underneath the pleura and epicardium.

Diagnosis

These two cases fall into our first classification of "status thymical lymphaticus, with suffocation and asphyxia from tracheal compression by an enlarged thymus gland."

Unfortunately, these glands were not weighed at the time of autopsy and no microscopic sections were taken.

CASE 3.—This pair of twin boys were, excepting for the multiple birth, normal deliveries after a full-term pregnancy. They were observed by their pediatrician first to have had a respiratory difficulty with moderate cyanosis at times at the age of 4 months. Otherwise, they were well nourished, had no feeding problems or other evidences of disease or congenital anomalies. Because of the respiratory distress, tracheal compression by enlarged thymus glands was suspected and, by x-ray pictures, proved. A course of therapeutic x-ray exposures was started immediately upon each child and toward the termination of the series of exposures their symptoms began to recede and after approximately four months had disappeared completely. These boys are now well, normal in every respect and now show no evidences of lymphatism or of developing allergy.

DISCUSSION

Such parallelism in two pairs of twins and one pair of brothers, four years apart, is more than pure coincidence, and it is our conviction that such correlation between siblings would be far more common were it looked for. The similarity both of the clinical and pathological pictures in these cases is striking and the relative age at which the enlarged glands began to cause respiratory difficulty is consistent with the many other solitary cases of Status Thymical Lymphaticus, both reported and unreported in our series.

PRECOCITY

In the autopsies done on our series of cases, no clinical evidences of precocity have been found associated with enlarged thymus glands or with medium-sized glands associated with adrenal gland changes. We have at times, however, encountered specific changes in the female gonads, although no changes in the testicles have been found. In approximately 3 per cent of the ovaries taken from babies in this series, there have been abnormal developments of the germinal epithelium with ovulation apparently progressing and a cumulus oophorus in a moderately large cystic cavity is not an uncommon sight in ovaries of children with enlarged thymus glands (Fig. 11). In addition, in these apparently functionating gonads, there is already a cystic development with small cysts filled with a clear white fluid and lined with a cuboidal layer of epithelium which is cytologically consistent with the epithelial cysts seen in later life, although of course in later life these cysts are considerably larger (Fig. 12). We have not encountered either this ovarian activity or the cystic development in necropsies done on babies with normal thymus glands dying from varieties of other causes, excepting congenital diabetes, but this may be a matter of coincidence. But we have seen them in girl babies running from the day of birth up to 5 months of age, running from the day of birth onward, and while this may be merely coincidental or only of pass-

*Personal communication, Dr. Charles B. Reeves, Oakland Coroner's Office, Oakland, Calif.

ing interest as these findings are associated with the thymus gland, it does unquestionably display one cause of both so-called follicular and simple epithelial cysts in the ovaries as they are seen later in adult women.

Summary

Sudden death in children resolves itself as a problem into many components. There is, of course, no one cause and in a series of well over 500 autopsies in children dying suddenly, the thymus problem is a secondary one. Strangely, however, enlargement of the thymus gland, lymphatism, hypo-adrenalism, and similar related conditions have been displaced even from secondary positions of importance as causes of disease and death and thrown into disrepute by articles in the medical literature which are based more on precedent and fashion than upon observation.

The now popular attitude that there is no such thing as Status Thymical Lymphaticus can be quickly dissipated by autopsy studies in any Coroner's Office where children are studied and the widespread belief that an enlarged thymus in itself will not cause asphyxia by tracheal and auricular compression and distortion, can be disproved at necropsy wherever studies are done on cases of sudden death in children.

On the other hand, when once accepted, Status Thymical Lymphaticus and related terms become far too easy to use. Instead of being reserved for specific cases to which they properly apply, such diagnoses are generically used to explain many sudden deaths in children, where there is no other obvious cause. It may be that such diagnostic abuses have in the main been responsible for the disrepute of the thymic status.

We now feel that an orderly necropsy proceedings will segregate the various causes of asphyxia in infants which is by far the commonest cause of sudden death under the age of 2 years and that such studies will, in their natural evolution, re-establish the relationship of enlarged thymus glands, lymphatism, adrenal hypoplasia, and such conditions either isolated or related as veritable and tenable direct and sole causes of death.

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PRODUCTION OF ACIDOSIS IN PREMATURE INFANTS BY PROTEIN MILK

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THE following study arose out of the chance observation that protein milk powder induced profound symptoms of acidosis in an otherwise normal premature infant. This observation has been confirmed by experimental trial in five other premature infants. Metabolic studies show that the acidosis is due to retention of chloride and can be prevented by the addition of sodium bicarbonate to the mixture. In the development of the acidosis, the balance studies demonstrate that intracellular sodium is transferred in considerable quantities to the extracellular fluids. The quantity involved equals about one-seventh of total extracelluar sodium and has not been usually taken into account in describing the factors which prevent wide fluctuations in the acid-base equilibrium of extracellular fluids. If further studies show that a similar transfer takes place in other types of acidosis, present concepts of the amount of sodium lost in acidosis have been seriously underestimated.

Methods.—The chemical methods[1] are those used previously in this laboratory. The pH was measured with a glass electrode at 38 degrees. In the balance experiments samples of the food, urine, and stools were analysed in duplicate. Stools were marked off with carmine. Urine specimens were collected over the period of time without catheterization. Samples of serum were collected under mineral oil.

NORMAL SERUM ELECTROLYTE IN PREMATURE INFANTS

Table I shows two average figures of serum analyses taken from five premature infants while receiving two slightly different milk mixtures. At birth

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TABLE I. ACID-BASE EQUILIBRIUM IN FIVE THRIVING PREMATURE INFANTS

FOOD	AVERAGE WEIGHT Gm.	CONCENTRATIONS PER LITER OF SERUM pH	HCO_3 mM	Cl mM	Na mM	K mM	Protein Gm.
Standard	2,120	7.38	22.5	103.0	140.0	5.8	50.6
S. D.		±0.04	± 0.2	± 3.1	± 1.7	±0.4	± 0.4
$NaHCO_3$	2,430	7.37	22.1	103.1	141.0	5.9	52.0
S. D.		±0.06	± 1.6	± 2.6	± 1.5	±0.5	± 0.2

S. D. = Standard deviation.

the babies weighed from 1,400 to 2,200 Gm. (average 1,930) and at the time of the first sample their ages varied from 26 to 89 days (average 43); their average weights are given in the table. The standard food was cow's milk with 2 per cent fat and 10 per cent added dextrimaltose. After the first blood sample, this mixture was modified by the addition of 0.9 Gm. of sodium bicarbonate per liter and the modified mixture was fed for an average of ten days (from 4 to 14 days) before the second sample was taken. All infants gained and looked well. The bicarbonate was added in order to rule out any possible acidotic effect of the usual cow's milk mixture. It will be be seen that the two values are statistically the same and probably can be considered normal for premature infants.

PRODUCTION OF CLINICAL AND CHEMICAL ACIDOSIS BY PROTEIN MILK POWDER

The following protocols illustrate that the administration of protein milk powder* induces chemical acidosis which is accompanied by loss of weight, pallor, anorexia, and weakness. In some cases typical Kussmaul breathing occurs. In the first case, the original observation was made because symptoms of acidosis developed following the use of protein milk powder in treating a mild diarrhea. In this patient protein milk powder was given again, when there was no diarrhea, in order to confirm this observation. Two additional babies were given protein milk powder with the production of chemical acidosis and this observation is confirmed by three other cases illustrated by balance studies in the next section of this report. The data indicate that feeding of premature infants exclusively on protein milk powder probably always induces acidosis. In all the cases studied the infants were essentially normal except for prematurity and no evidences of renal disease were encountered.

CASE 1.—The baby was the second of white twins born Jan. 17, 1939. The first twin was born by version and extraction and never breathed spontaneously. Autopsy showed congenital stenosis of the mitral and aortic valves with hypertrophy of the left auricle and ventricle. The twins were not identical and the patient under consideration showed no abnormalities. At birth the weight was 2,000 Gm. and the length, 44.5 cm. He was fed a mixture of milk with 2 per cent fat and 10 per cent added dextrimaltose, the caloric intake being gradually increased to about 120 per kilogram by the ninth day. From the tenth to twentieth day of life, he had from five to eight somewhat loose stools each day and gained little weight. At this time the weight was 2,140 Gm. and the food was changed to protein milk powder, 23 Gm. in 160 c.c. of water. Two days later the stools were better, but the weight decreased to 2,010 Gm. The food was increased to protein milk powder 45 Gm. in 280 c.c. of water. Additional water was given to make the water intake over 150 c.c. per kilogram and as high as 200 c.c. per kilogram on some days. On February 13, the sixth day of protein milk feeding, the baby looked sick and pale but not dehydrated. The weight remained the same during the last two days on protein milk. Finally marked Kussmaul breathing developed. In the development of this picture there was no diarrhea and the urine gave

*In all the studies protein milk powder (Mead Johnson and Company) was used. This product is made by precipitation of caseine with calcium chloride rather than rennet. The modification was introduced by Finkelstein and produces a product of slightly different composition from that of the original Eiweiss milk. The manufacturer is making a suitable modification so as to do away with the factor responsible for the production of acidosis.

no tests for acetone. Clinical recovery was prompt following an intravenous injection of 2 Gm. of sodium bicarbonate together with clyses of artificial interstitial salt solution. When the baby was 8 weeks old (March 14), protein milk powder, 70 Gm. in 480 c.c. of water was given for four days. During this period the weight decreased from 2,890 to 2,660 Gm. The boy at this time (March 18) looked sick but did not develop Kussmaul breathing. After receiving a clysis of salt solution and the usual feedings, the baby was discharged apparently well four days later. The development of acidosis is shown in the following serum analyses:

Date	2/13/38	2/14	2/15	3/14	3/18	3/19	3/20
HCO_3 meq. per liter	3.6	10.4	19.3	9.4	6.5	15.6	19.8
Cl meq. per liter	123	118	115	108	115	112	
Na meq. per liter		148					

The specimen on February 13 was taken during the initial acidosis following six days on protein milk; the specimen taken March 18 was taken after the second period of four days on protein milk.

In this case it should be noted that there is low bicarbonate and high chloride on March 14 when the infant was taking what has been considered an appropriate food for premature infants together with sufficient water to yield 140 or more cubic centimeters of water per kilogram. The other data show that the high chloride is rather persistent despite restoration of serum bicarbonate with sodium bicarbonate after the first period on protein milk and also after clyses of artificial interstitial salt solution after the second period of feeding with protein milk powder. The urine specimens revealed no albumin or abnormal sediment. The specific gravity was never determined. Subsequent course indicates that the baby was a normal premature infant.

CASE 2.—The baby was a white boy born April 28, 1943, after an estimated gestation of eight months. One week before delivery the mother developed albuminuria and high blood pressure. The delivery was spontaneous and no trouble was encountered with the baby. Weight at birth was 2,000 Gm.; length, 44 cm. During the first nine days he was fed cow's milk with 2 per cent fat and 10 per cent added dextrimaltose, at caloric intakes gradually increasing to 90 per kilogram. He was then changed to the same number of calories of protein milk powder made up so as to contain 90 calories per 100 c.c. On the original food mixtures, the weight was 2,125 Gm. on May 8, and the change to protein milk was made at this time. By May 11 he weighed 1,930, a loss of about 10 per cent of the body weight. At this time the baby looked pale and dehydrated. There was no Kussmaul breathing. After a clysis of interstitial salt solution the child was fed the original feeding and thrived, weighing 2,500 Gm. on the twenty-eighth day of life when he was discharged. The development of acidosis is shown in the following serum analyses:

Date	5/8/42	6/11/42
HCO_3 meq. per liter	15.4	7.8
Cl meq. per liter	107	104
Protein per cent	5.5	5.8
pH	7.45	7.35
N.P.N. mg. per cent		43

CASE 3.—The baby was a Negro boy born after an estimated gestation of eight months. No cause for the premature delivery was apparent. The delivery was spontaneous and no trouble was encountered with the baby at the time of birth. The birth weight was 1,450 Gm.; length, 40 cm. On the second day of life the baby was fed a mixture of cow's milk with 2 per cent fat and 10 per cent added dextrimaltose, increasing the caloric intake gradually during the first nine days to about 110 per kilogram. Ascorbic acid (25 mg.), thiamine (1 mg.), riboflavin (2 mg.) and irradiated ergosterol (Drisdol) were added to the mixture after the fourteenth day. He thrived and was discharged on the seventieth day weighing 2,600 Gm.

On the thirty-fourth day the baby weighed 1,875 and was changed to an isocaloric amount of protein milk powder (45 Gm. in 240 c.c. of water). Four days later he weighed 1,750 Gm. (a loss of about 10 per cent in weight). There had been from four to five pasty stools each day. He looked pale and "dehydrated," but there was no Kussmaul breathing. Recovery was rapid after a clysis and return to the previous food mixture.

The development of acidosis is illustrated by the following serum analyses:

Date	5/12/42	5/16/42
HCO_3 meq. per liter	21.5	8.5
Cl meq. per liter	108	132
Protein per cent	4.35	5.34
Na meq. per liter	134	139
K meq. per liter	5.1	6.1
pH	7.39	7.01
N.P.N. mg. per cent	27	125
Serum P mg. per cent		8

In Cases 2 and 3, the caloric intake and concentration were the same as during the control period. No diarrhea or decrease in water intake occurred to explain the development of acidosis. The acidosis is characterized by high concentration of chloride in Cases 1 and 3 but not in Case 2. This patient, however, showed the least disturbance. In Case 3, serum nonprotein nitrogen was high. The mechanism of these changes will be brought out by the metabolic studies.

That the particular mixture of protein, fat, and carbohydrate is not the sole cause of the difficulty is illustrated by the following case.

CASE 4.—The boy was born Dec. 31, 1943, weighing 1,915 Gm. and measuring 41 cm. He was fed cow's milk with 2 per cent fat and 10 per cent added carbohydrate gradually increasing the intake to 120 calories per kilogram by the fourteenth day. On the thirty-second day the food was changed for a week to an isocaloric mixture—protein milk powder 45 Gm. plus sodium bicarbonate 0.9 Gm. in 240 c.c. of water. The weights at the beginning and end of the feeding on protein milk powder were 2,280 and 2,270 Gm. Outside of looking a little pale, nothing abnormal was noted at the end of the period. The baby was discharged on the forty-seventh day weighing 2,510 Gm.

The serum findings were as follows:

Date	2/1/44	2/8/44
HCO_3 mM per liter	25	19
Cl mM per liter	102	102
Na mM per liter	144	140
K mM per liter	5.1	5.3
Protein Gm. per liter	43.5	49.3
pH	7.38	7.38

The addition of sodium bicarbonate was sufficient to prevent serious electrolyte disturbance. This finding is confirmed by a metabolic study in the following section of the paper. It should be noted, however, that the baby did not gain and it is doubtful if the baby could thrive on this food.

BALANCE STUDIES

The balance studies were designed to show what disturbances in electrolyte balance appear (1) during feeding with protein milk powder (Tables II, III, and VI) (2) during feeding with protein milk powder plus $NaHCO_3$ (Table IV) (3) during feeding with HI-PRO,* which is similar to protein milk powder as to organic but not electrolyte content (Table V) and (5) during feeding with cow's milk with 2 per cent fat and 10 per cent added carbohydrate (Table II). Table VII shows serum analyses taken at the beginning and end of the balance periods. Protocols are given at the end of this paper.

Examination of the tables shows that feeding with protein milk powder leads to excessive retention of chloride in relation to other constituents, particularly sodium. In Table II, a retention of 13 mM of chloride is shown during a period when 8 mM of sodium were lost; in Table III, 20 mM of

*HI-PRO is a mixture of powdered whole milk and separated milk from which some lactose has been removed. It is supplied by Special Milk Products, Inc.

chloride were retained while negligible amounts of sodium were retained; in Table VI, 14 mM of chloride were retained during negligible changes in body sodium when protein milk powder alone was given. Since this period followed the retention of 9 mM of chloride during feeding with protein milk powder plus dextrimaltose, the combined gain was 23 mM of chloride for the two periods

TABLE II. BALANCE IN CASE 5 (TWO PERIODS OF THREE DAYS)

	H_2O Gm.	Solids Gm.	Fat Gm.	N Gm.	Cl mM	Na mM	K mM	P mM	Ca mM
				Half Skimmed Cow's Milk Plus 10 Per Cent Dextrimaltose					
Intake	656	154	16	4.0	21.7	17.5	34.3	24.3	25.1
Urine	465	7		1.97	18.5	10.8	25.8	9.5	0.4
Stools	28	7	3.0	0.41	0.5	0.1	1.9	7.1	18.0
Output	493	14		2.38	19.0	10.9	27.7	16.6	18.4
Balance	163			1.62	2.7	6.6	6.6	7.7	6.7
				Protein Milk Powder					
Intake	644	119	32	6.13	40.2	14.9	33.3	39.0	54.6
Urine 1	151			1.08	7.2	7.0	6.2	4.2	0.2
Urine 2	148			1.28	9.1	8.4	6.3	4.9	0.1
Urine 3	128			1.28	8.9	6.3	5.0	3.4	0.1
All urine	427			3.64	25.2	21.7	17.5	12.5	0.4
Stools	56	14	9.7	0.66	1.7	1.0	4.0	7.2	28.0
Output	483			4.30	26.9	22.7	21.4	19.7	28.4
Balance	161			1.83	13.3	−7.8	11.8	19.3	25.2

First Part: Initial and final body weights 2.16 and 2.26 kg. (May 22 to 25).
First Part, Food: Milk with 2 per cent fat and 10 per cent added dextrimaltose; six feedings of 45 c.c.
Second Part: Initial and final body weights 2.26 and 2.075 kg. (May 25 to 28).
Second Part, Food: Protein milk powder 50 Gm., water 270 c.c.; six feedings of 45 c.c.

TABLE III. BALANCE IN CASE 6 (TWO DAYS)

	H_2O Gm.	Solids Gm.	Fat Gm.	N Gm.	Cl mM	Na mM	K mM	P mM	Ca mM
				Protein Milk Powder					
Intake	487	103	27	5.23	34.3	12.7	28.4	33.3	46.6
Urine	148	2		1.47	10.6	7.1	8.2	7.9	
Stool	135	16	11.5	0.98	3.4	3.8	10.2	6.6	35.1
Output	283	18		2.45	14.0	10.9	18.2	14.5	35.1
Balance	204			2.78	20.3	1.8	10.2	18.8	11.5

Initial and final body weights 2.45 and 2.40 kg. (Dec. 8 to 10).
Food: Protein milk powder 70 Gm., water 330 c.c.; six feedings of 50 c.c.

TABLE IV. BALANCE IN CASE 7 (THREE DAYS)

	H_2O Gm.	Solids Gm.	Fat Gm.	N Gm.	Cl mM	Na mM	K mM	P mM	Ca mM
				Protein milk powder plus $NaHCO_3$					
Intake	614	121	32	6.52	36.0	43.0	29.9	36.0	55.7
Urine	293	7		2.78	21.8	23.3	19.2	13.4	
Stool	89	22	10.6	0.95	0.8	4.2	6.8	6.8	27.2
Output	382	29		3.73	22.6	27.5	26.0	20.2	27.2
Balance	232			2.79	13.4	15.5	3.9	15.8	28.5

Initial and final body weights 2.085 and 2.080 kg. (Feb. 21 to 24).
Food: Protein milk powder 50 Gm.; $NaHCO_3$, 0.9 Gm.; water 260 Gm.; eight feedings of 30 c.c.

TABLE V. BALANCE IN CASE 8 (THREE DAYS)

	H_2O Gm.	Solids Gm.	Fat Gm.	N Gm.	Cl mM	Na mM	K mM	P mM	Ca mM
				HI-PRO Milk					
Intake	607	113	16	7.32	30.1	24.3	33.4	33.1	36.0
Urine	380	10		4.0	21.7	11.3	25.1	12.8	
Stools	67	13	5.7	0.75	0.6	0.7	4.1	10.0	23.2
Output	447	23		4.75	22.3	12.0	29.2	22.8	
Balance	160			2.57	7.8	12.3	4.2	10.3	12.8

Initial and final body weights 2.28 and 2.255 kg. (May 30 to June 2).
Food: HI-PRO 60 Gm., water 300, eight feedings of 30 c.c.

in this infant. Addition of carbohydrate to protein milk powder did not do away with the abnormal retention of chloride (Table VI, first part) but the retention was definitely less than when protein milk powder alone was used. These findings are sufficient to explain the decrease in concentration of serum bicarbonate and the increase in concentration of serum chloride shown in Table VII.

TABLE VI. BALANCE IN CASE 9 (TWO PERIODS OF THREE DAYS)

	H_2O Gm.	Solids Gm.	Fat Gm.	N Gm.	Cl mM	Na mM	K mM	P mM	Ca mM	pH
				Protein Milk Powder Plus Dextrimaltose						
Intake	765	168	24	5.56	29.0	11.8	22.6	28.8	40.0	
Urine	434	6.5		2.08	19.0	12.0	11.8	8.5		5.09
Stool	73	18.8	8.9	0.48	0.7	0.8	8.3	9.1	27.5	
Output	507	25.3		2.56	19.7	12.8	20.1	17.6		
Balance	258			3.0	9.3	− 1.0	2.5	11.2	12.5	
				Protein Milk Powder						
Intake	752	148	35	8.90	43.7	16.5	29.6	44.5	66.0	
Urine	336	9		1.17	24.8	15.0	10.6	17.3		5.65
Stools	133	32	25	1.01	4.6	2.5	17.4	13.1	42.0	
Output	499	41		2.18	29.4	17.5	28.0	30.4		
Balance	236			6.72	14.3	− 1.0	1.6	14.1	24.0	

First Part: Initial and final body weights 2.48 and 2.35 kg. (April 24 to 27).
First Part, Food: Protein milk powder 40 Gm., dextrimaltose 35 Gm. and water 340 c.c.; six feedings of 50 c.c.
Second Part: Initial and final body weights 2.35 and 2.35 kg. (April 27 to 30).
Second Part, Food: Protein milk powder 67 Gm., water 340 c.c.; six feedings of 50 c.c.

TABLE VII. SERUM CONCENTRATION PER LITER

CASE	TABLE	DATE	HCO_3 mM	Cl mM	Protein Gm.	Na mM	K mM	H_2O Gm.	pH
5	II	5/25	17.0	114	32	140	4.4		7.29
5	II	5/28	9.3	116	59	132	3.4		7.22
6	III	12/8	14.0	97	72				
6	III	12/10	12.0	116	53	139	5.3		
7	IV	2/21	21.0	106	46	139	4.9		7.47
7	IV	2/24	18.4	106	49	144	5.1		7.33
7	IV	3/1	19.3	96					7.26
8	V	5/30	21.3	100	62	139	6.6	934	7.36
8	V	6/2	16.9	104	62	135	7.6	932	7.33
9	VI	4/24	21.0	110	61	134	6.1	940	7.30
9	VI	4/27	17.5	115	60	131	6.0	938	7.24
9	VI	4/30	8.8	122	48	137	4.8	938	7.18
9	VI	5/2	15.0	122					7.29

Similar retention of chloride without sodium was not obtained with HI-PRO (Table V) or half skimmed milk with added carbohydrate (Table II). The addition of sodium bicarbonate to protein milk powder (Table IV) led to rather large retentions of both sodium and chloride but no disturbance in the relationships of these retentions to each other and hence to no serious disturbance in acid-base equilibrium of extracellular fluids.

All the periods show positive balances of nitrogen, phosphorus, and calcium which do not exhibit great disturbances in the relation of these elements to each other.

In the tables the balances of water do not take into account the water formed by metabolizing the food nor the imperceptible water loss, but they are of an order of magnitude which indicates that the imperceptible loss is from 40 to 60 c.c. per kilogram of body weight per twenty-four hours.

Attention is directed to the large loss of fat in the stools during the periods of feeding with protein milk powder and HI-PRO. The stool fat equals about one-third of the ingested fat except in the last period of Table VI when it is

three-quarters. Thus the failure of fat absorption may be aggravated by severe acidosis but the measures which prevent acidosis do not give normal fat absorption.

INTERPRETATION OF THE BALANCES IN TERMS OF NORMAL TISSUES

Muscle constitutes about 40 per cent of body weight and in normal cats, rats, and monkeys[1] 1 kg. of fat-free muscle contains about 33 Gm. of nitrogen and 105 mM of potassium and 67 mM of phosphorus. The calcified material of bone contains about 0.57 mM of phosphorus for each millimole of calcium.[2] Since the other parenchymatous tissues are relatively small in amount and have compositions which do not vary widely from muscle, intracellular phosphorus and potassium can be predicted from the storage of nitrogen and calcium. The following equations give the predicted balances based on the compositions mentioned:

$K_c = 3\ N_b$ Calculated potassium of muscles from balance of nitrogen.
$P_c = 2\ N_b + 0.57\ Ca_b$ Calculated phosphorus of muscle from balances of nitrogen and calcium.

Electrolyte is expressed in millimoles and nitrogen in grams.

The calculations merely define the amounts of phosphorus and potassium, which give retentions which enable the body to keep a relatively normal composition. They do not take into account abnormal distributions nor disproportions in the relative rates of growth of various tissues. However, the calculations make it possible to detect gross abnormalities in the relative retentions of nitrogen, phosphorus, and potassium.

Extracellular fluids constitute about 25 per cent of a normal baby and these fluids contain Cl and Na at concentrations of about 115 and 143 mM per kilogram. Hence the amounts of extracellular chloride and sodium in the body equal the volume of extracellular fluids times the concentrations given. If all chloride and sodium remain extracellular and the composition remains normal, the following equation should hold:

$Cl_c = 0.77\ Na_b$ Calculated chloride from the balance of sodium.

This equation assumes that both ions remain essentially extracellular. This is approximately true of chloride,[3] but considerable amounts of sodium are in the calcified material of bones and in the intracellular phase of muscle. The sodium associated with calcium may be neglected since only 1 mM of sodium is associated with 30 mM of Ca.[2] The subject of intracellular sodium is covered more fully in the subsequent sections. It will suffice here to state that intracellular sodium would not be a big factor in short-time experiments if the tissues remain of constant composition.

Based on the factors we have discussed, Table VIII compares the calculated normal total composition of the muscle and extracellular fluids with the difference between the balance and the calculated requirement. A positive value for this difference indicates excessive retention of chloride in extracellular fluid or potassium and phosphorus in intracellular fluids. A negative value indicates relative deficit. The magnitude of the change is indicated by comparison with the normal content. It must be kept in mind that the calculations do not take into account a relative disproportion in the retention of extracellular and intracellular ions but merely indicate the discrepancy in retentions in extracellular or intracellular fluids in relation to their normal compositions.

TABLE VIII. MEASURE OF ABNORMAL COMPOSITION OF TISSUES.

CASE	BALANCE PERIOD		BALANCE MINUS CALCULATED REQUIREMENT			TOTAL EXTRACELLULAR		MUSCLE	
	TABLE	FOOD	Cl mM	P mM	K mM	Cl mM	Na mM	K mM	P mM
5	II	Half skimmed milk	− 2.4	0.7	1.7	62	77	91	68
5	II	Protein milk powder	19	1.0	6.5	62	77	91	68
6	III	Protein milk powder	18.9	6.6	1.9	70	88	113	76
7	IV	Protein milk powder + $NaHCO_3$	1.5	− 6.0	− 4.6	60	75	87	65
8	V	HI-PRO	− 1.7	− 2.1	− 3.5	66	82	96	71
9	VI	Protein milk powder + CHO	10	− 1.9	− 6.5	71	89	104	77
9	VI	Protein milk powder	15	−13	−18.5	71	89	104	77

P requirement = $0.57(Ca)_b+2(N)_b$
K requirement = $3(N)_b$
Cl requirement = $0.77(Na)_b$
$(Ca)_b$, $(N)_b$ and $(Na)_b$ refer to the respective balances.
A positive value in the table indicates excessive retention; a negative value, relative deficit.

The patients receiving protein milk and developing acidosis all retain enough chloride in relation to sodium to make the extracellular chloride about one-third too high (Cases 5, 6, and 9). While the patients receiving half skimmed milk, HI-PRO and protein milk powder with added sodium bicarbonate retained a good deal of chloride, enough sodium is also retained to leave the relative retentions of chloride approximately normal (Cases 5, 7, and 8). In the cases developing acidosis, Table VII does not show that the chloride rose as high in concentration as these calculations predict. The subsequent section takes into account the possibility of shift of intracellular sodium to extracellular fluids and shows that this shift must occur and is of a magnitude that can be accounted for by amounts of intracellular sodium found by tissue analyses.

The phosphorus and potassium changes shown in Table VIII are probably too small to be interpreted except in Case 9. This patient was subjected to acidosis for six days instead of three and developed greater clinical disturbances. For this reason, the relative deficit of intracellular phosphorus and potassium is regarded as a valid finding representing an advanced stage of acidosis.

INTERPRETATION OF BALANCES IN TERMS OF DISTRIBUTION OF BODY WATER AND ELECTROLYTE

In order to bring into view the changes in distribution of sodium and potassium, the following assumptions were made (1) that a baby with normal water balance has extracellular fluids equal to about 25 per cent of the body weight, (2) that the concentration of chloride and sodium in a serum ultrafiltrate measures the average concentration in extracellular fluids, (3) that the balance of chloride measures the change in total extracellular chloride. Indicating amounts with parentheses ( ) and concentrations by brackets [ ], the following equations are self-explanatory:

(Initial Extracellular H_2O) [Initial Extracellular Cl] = (Initial Extracellular Cl)
(Initial Extracellular Cl) + (Balance Cl) = (Final Extracellular Cl)
(Final Extracellular Cl) ÷ [Final Extracellular Cl] = (Final Extracellular H_2O)
(Initial Extracellular H_2O) [Initial Extracellular Na] = (Initial Extracellular Na)
(Final Extracellular H_2O) [Final Extracellular Na] = (Final Extracellular Na)

(Initial Extracellular Na) − (Final Extracellular Na) = (Balance Extracellular Na)
(Balance Extracellular Na) + (Balance Na) = (Cellular Balance Na)

Water is expressed in kilograms, amounts of electrolyte in millimoles and concentrations in millimoles per kilogram of water. The cellular balance of sodium is negative when sodium leaves intracellular fluids and is positive when sodium enters intracellular fluids. Similar equations were also used for potassium. In the case of balance of intracellular potassium, two figures are given. The first is figured like the sodium and represents the absolute balance. However, if protein is stored in muscle, 3 mM of potassium will be retained in the muscle for each gram of nitrogen. The figure in the next to the last column takes into account this relationship. This figure, therefore, represents the change of muscle potassium relative to total nitrogen. In order to calculate intracellular water, changes in weight were considered to be entirely due to changes in water. This procedure would be theoretically less desirable than calculated water balance except for the fact that the latter requires the uncertain values for imperceptible loss and total metabolism. The difference between the calculated change in extracellular water and the change in total water is balanced in the table by a change in intracellular water.

TABLE IX. DISTRIBUTION OF TISSUE WATER AND ELECTROLYTE

CASE	BALANCE PERIOD* TABLE	FOOD	WEIGHT CHANGE Gm.	TOTAL EXTRACELLULAR H_2O Gm.	Cl mM	Na mM	K mM	BALANCE INTRACELLULAR H_2O Gm.	Na M	K M	K† M	N Gm.
5	II	Start		540	(62)	(77)	(2.3)					
5	II	Half skimmed milk	100	530	(65)	(76)	(2.3)	(110)	(7.6)	(7.7)	(2.9)	1.6
5	II	Protein milk powder	−185	610	78	81	2.0	−265	−12.8	12.2	6.8	1.8
6	III	Start		610	66	(87)	(3.5)					
6	III	Protein milk powder	− 50	670	86	(95)	(3.5)	(−110)	(−10.2)	(10.2)	(2.4)	2.8
7	IV	Start		520	61	74	2.5					
7	IV	Protein milk powder + $NaHCO_3$	− 5	630	74	92	3.2	−115	−2.5	3.1	−5.3	2.8
8	V	Start		570	63	81	3.8					
8	V	HI–PRO	− 25	610	71	85	4.6	− 65	8.3	3.4	−4.4	2.6
9	VI	Start		620	76	85	3.8					
9	VI	Protein milk powder + CHO	−130	670	85	89	4.0	−180	−5.0	2.3	−6.7	3.0
9	VI	Protein milk powder		730	99	102	3.5	− 60	−14.0	2.1	−17.9	6.7

*The values labeled "Start" are based on the initial serum concentrations and an assumed initial value for extracellular water. The second set of values is based on the balances and the serum concentrations at the end of the balance period. In Cases 5 and 9, the third set of values is based on the final balance period and the final serum concentrations.

†Corrected balance of potassium [$Kc = -3(N)_b$] indicating intracellular balance in relation to balance of N.

Figures in parentheses are based on assumed normal values for serum Cl or Na at the time when usual diet was being taken.

Table IX shows the factors calculated by this scheme. The patients developing acidosis (Cases 5, 6, and 9) all show both a considerable increase in extracellular water and a loss of weight. Hence there is a fairly large loss of intracellular water. The patients receiving protein milk powder with added sodium bicarbonate and HI-PRO (Cases 7 and 8) also show increases in extracellular water and decreases in intracellular water. The chief difference is that the patients developing acidosis transferred considerable amounts of intracellular sodium to extracellular fluids. Those not developing acidosis showed negligible change in intracellular sodium in Case 7 and a positive balance in Case 8. In Case 8, the positive balance of intracellular sodium apparently displaced a little intracellular potassium as indicated by a negative balance of potassium in relation

to nitrogen (See the next to last column). Cases 5 and 6 show considerable positive balances of potassium but the balance is small in relation to nitrogen retention. Hence the loss of intracellular sodium is not primarily related to increase in intracellular potassium. This view is clearly brought out in Case 9 where large amounts of intracellular sodium were lost at the same time that a relative deficit of potassium and phosphorus was developing.

Attention is directed to the fact that the loss of intracellular water is not explained by the amounts of the decrease in intracellular cations nor by the increase in concentration of extracellular cations. One must assume that the osmotic activity of some compounds in the cells is so altered as to make water available to extracellular fluids. It is striking that these patients lost weight and showed many of the symptoms of "dehydration," but the decrease in water is intracellular while extracellular water is greater than normal. This picture is the opposite from that produced by loss of extracellular electrolyte without water[4] which is probably more characteristic of many types of clinical dehydration. The data clearly show that loss of intracellular water may account for a great deal of water loss independent of loss of potassium.

THE FACTOR IN COMPOSITION OF PROTEIN MILK POWDER RESPONSIBLE FOR ACIDOSIS

In comparing various infant foods for the factor responsible for the abnormal retention of chloride, it was deemed best to reduce all concentrations to amounts per 100 calories. This procedure is justified by the fact that caloric intake is the chief determinant of the amount of food eaten. As shown in Table X, the chief difference between protein milk powder and the other

TABLE X. CONTENT OF INFANT FOODS PER ONE HUNDRED CALORIES

FOOD	PROTEIN Gm.	FAT Gm.	CARBOHYDRATE Gm.	Cl mM	Na mM	K mM	P mM	Ca mM	(Cl–Na) mM
Human	1.84	5.2	11.0	1.5	0.7	1.8	0.7	1.3	0.8
Cow	5.2	5.3	7.2	5.0	4.0	6.0	4.4	4.6	1.0
HI–PRO	8.8	2.8	9.8	4.8	4.1	5.1	5.9	6.5	0.7
½ Skimmed milk + CHO	3.4	2.2	16.0	3.0	2.4	4.6	3.3	3.4	0.6
Finkelstein's milk	8.4	5.9	4.0	5.4	3.9	4.7	6.1	6.2	1.5
Protein milk powder	7.3	5.3	4.8	5.7	2.0	3.8	5.9	8.8	3.7
Protein milk powder + $NaHCO_3$	7.3	5.3	4.8	5.7	7.3	3.8	5.9	8.8	–2.0
Protein milk powder + CHO	4.6	3.1	13.2	3.1	1.1	2.1	3.2	4.7	2.0

The values for human and cow's milk are taken from Shohl, A. T.: Mineral Metabolism, New York, 1939, Reinhold Publishing Corporation, p. 73. The other analyses were made in the pediatric chemical laboratory.

foods is the relative excess of chloride over sodium and calcium over phosphorus. The excess is about 3 mM of each per 100 calories. If 2 mM of calcium is added to the values for Finkelstein's protein milk and 2 mM of sodium subtracted, the figures approximate those for the protein milk powder. Presumably the production of acidosis is dependent on the failure of the kidneys to meet this added load. Actually the amount of electrolyte which a given food requires the kidney to excrete is the difference between the intake and the required retentions plus the stool contents. In the present experiments the urinary excretions do not differ greatly with respect to the acid-base balance except in Case 9. The retentions of chloride, therefore, seem related to the relative deficit of sodium which makes excretion of chloride difficult. That the failure is chiefly renal is supported by the fact that the contents of nitrogen, fat, carbohydrate, phosphorus, and calcium are the same in foods that cause

acidosis as in some which do not cause acidosis. Hence it is safe to conclude that protein milk powder contains too much chloride in relation to sodium to be excreted by premature infants.

As was previously pointed out protein milk powder is not quite the same as the original Finkelstein protein milk. The analysis of Finkelstein's protein milk which was made up especially for the analysis shows the same peculiarity (excess of chloride over sodium) but to a less degree. The difference is explained by the fact that the original Finkelstein's protein milk is prepared by rennet while protein milk powder is prepared by precipitating the casein with calcium chloride. In this process some calcium is apparently added to the final product and some sodium is drained off as sodium chloride. The end result is much the same as addition of calcium chloride which has been shown by Gamble and associates[5] to induce acidosis.

DISCUSSION

The data we have given prove without doubt that protein milk powder even modified by the addition of carbohydrate is not a suitable food for premature infants. Addition of about 22 mM of $NaHCO_3$ (1.77 Gm.) per 100 Gm. of dried material will prevent acidosis. While protein milk alone is seldom used to cover the complete caloric requirement and has not been recommended for premature infants, its use entails dangers of which the authors were unaware. Addition of carbohydrate only makes protein milk powder have slightly less tendency to produce acidosis. Even in older infants a modified form containing more sodium relative to chloride is indicated.

It is likely that the same phenomenon (acidosis produced by difficulty in excreting chloride without sodium) is exhibited by premature infants when given other foods. For years it has been the experience at the New Haven Hospital that premature infants who are not looking well and are not gaining regularly respond satisfactorily to a small clysis of physiological saline or preferably interstitial salt solution or Hartmann's lactate-Ringers. This observation was puzzling as long as a disturbance of extracellular electrolyte was regarded as likely to develop only as a result of vomiting, diarrhea, or abnormal renal function. It is now clear that premature and even normal newborn infants do not have as effective renal function as is developed later in life. Studies have shown that clearances of urea[6, 7] and inulin[8] in babies are low and that infants tend to retain chloride in spite of high concentration in the serum. This makes all infants but particularly premature ones vulnerable to small deviations in the intake of fixed anions and cations or small disturbances in their excretion such as accompany loose stools that would not cause trouble later in life.

Table X shows that excess of chloride over sodium is characteristic of all milks. In human milk little difficulty is encountered on this account because of the low electrolyte content. The phosphate of human milk, the other fixed anion which is, in part, excreted by the kidneys, is present in amounts which are barely sufficient for growth and hence urinary phosphate is minimal. Cow's milk is usually satisfactory from this point of view, especially when modified by addition of carbohydrate, unless other factors lead to loose stools containing more than the usual minimal amount of sodium and chloride. Finkelstein's original protein milk probably frequently causes trouble like that demonstrated for protein milk powder but to a less degree. Indeed Finkelstein[9] pointed out

that many physicians did not recommend protein milk in the first months of life and some thought it was contraindicated. While Finkelstein did not subscribe to this view, he advised that it always should be used with added carbohydrate which among other things diminishes the load of material to be excreted by the kidneys. Hoobler,[10] in studying the effects of high protein feeding, noted on the final days of feeding with protein milk that "the child no longer took an interest in his surroundings, and gradually went into a state of semistupor. The pulse was slower, and there were times when the respirations were slightly irregular. The stupor continued for a few days after the observations ceased." After the disturbance had developed on double albumin milk, Hoobler noted that recovery required several days of feeding with the usual diet. Although he thought that the condition was not due to acidosis, he based this conclusion on absence of Kussmaul breathing or ketosis. We know now that acidosis can only be excluded by determination of blood carbon dioxide and pH. Hoobler's description fits our observations almost exactly. Schoenthal[11] showed that very high calorie intake of dried milk in the usual amount of water produced acidosis. Branning[12] has observed acidosis frequently in premature infants receiving whole milk mixtures. In Table X the values for (Cl-Na) are given. If the excess of chloride over sodium is the most important factor in producing acidosis, protein milk powder, protein milk powder plus carbohydrate, Finkelstein's original protein milk, and undiluted cow's milk are, in this order, the ones most likely to cause acidosis. Only in the case of undiluted cow's milk is unmistakable evidence of production of acidosis in young babies lacking for these foods. Re-examination of foods for premature infants is indicated, keeping in mind the handicap to the adjustment of acid-base equilibrium which these infants exhibit.

In the present experiments urinary ammonia was not determined. However, previous work[13] indicates that increase in urinary ammonia only develops after an interval of one or two days. If it comes in infants, it is obvious that it is either too late or too ineffective to restore tissue electrolyte.

Certain writers[14] have been so impressed with the usual tendency of the kidneys to adjust acid-base equilibrium that it is assumed that sufficient sodium chloride and water will be adequate for the treatment of acidosis. The mechanisms of this adjustment have been best demonstrated in practically normal individuals and do not take into account the relative slowness of the process nor its failure when renal function is limited to that available in young or premature infants. Hartmann.[15] Darrow,[16] and Butler and Talbot[17] have emphasized that something more appropriate than salt solution should be used in many types of disturbance in electrolyte balance. The present data show that premature infants can hardly be expected to overcome acidosis expeditiously if treated with physiological saline alone. Hartmann's lactate-Ringer, sodium lactate, or interstitial salt solution are probably always indicated in premature and young infants requiring parenteral electrolyte.

The urine specimens of Case 9 were tested for parahydroxyphenyl acids and gave negative results (reduction of Fisk and Subbarow's phosphate reagent). Defect in handling certain amino acids as the result of a high requirement of ascorbic acid is not a likely cause of the acidosis.[18]

The present data are of great theoretic and practical importance since they demonstrate that intracellular sodium plays a significant rôle in the regulation of the acid-base equilibrium of the body. As was pointed out previously,[19] nor-

mal muscle potassium may vary from 44 to 48 mM per 100 Gm. of fat-free solids in rats while intracellular sodium varies between 1 and 4 mM per 100 Gm. of fat-free solids (100 Gm. of fat-free solids represent about 430 Gm. of fat-free muscle). Although these variations can occur without obvious disturbances, the higher values are the usual ones. If muscle represents about 40 per cent of the body weight and extracellular fluids about 25 per cent of body weight, intracellular sodium usually equals about one-tenth of total sodium in extracellular fluids. This is equivalent to over one-half of all the extracellular sodium normally present as bicarborate and, therefore, constitutes a large reservoir of sodium in support of lowered bicarbonate and a considerable one in relation to total extracellular sodium. The apparent transfer of intracellular sodium to extracellular fluids in the present study is about one-seventh of that of extracelluar fluids. Although other tissues besides muscle[20] are known to contain intracellular sodium, most of the transfer can be accounted for by the known amount in muscle.

It must be kept in mind, however, that the calculated shift of sodium from intracellular fluids is based on the assumption that the retained chloride remains extracellular. If some chloride becomes intracellular the shift of sodium would be less than calculated. The significance from the point of view of extracellular fluids would be much the same inasmuch as the relative deficit of sodium would be the same, or looking at the data from the other point of view, the relative excess of chloride is the same. The data indicate certainly that shift of chloride into cells or sodium out of the cells occurs. Further study may show both processes taking place at the same time. At present it seems less likely that large amounts of chloride become intracellular than that intracellular sodium becomes extracellular.

The present study shows the function of intracellular sodium in augmenting the concentration of extracellular sodium bicarbonate but under other circumstances sodium may be transferred to intracellular fluids so as to diminish the concentration of serum bicarbonate. This second type of function is clearly demonstrated in another paper[21] which reported the case of a patient suffering from profound alkalosis due to watery stools containing more chloride than sodium. As large losses of chloride developed, sodium entered the cells, displacing potassium. The exchange was large because large amounts of potassium were excreted. It is obvious that this transfer diminished the rise in serum bicarbonate which would have occurred if all sodium had remained extracellular. Displacement of muscle potassium by sodium has been demonstrated experimentally as a result of diets low in potassium[19, 22] or following injections of desoxycorticosterone acetate.[19, 23, 24] It may equal about one-half of normal muscle potassium; that is, it may be equivalent to one-half to two-thirds of the sodium normally present in extracellular fluids. This suggests that, with a small balance of sodium, the intracellular shift of sodium would be limited by the ability of the body to function with low extracellular sodium or by disturbances in the muscle or heart induced by loss of intracellular potassium. Future work will doubtless reveal many conditions in which sodium leaves or enters extracellular fluids owing to fluctuations in the amount of intracelluar sodium. In some cases the change is dependent on loss or gain of muscle potassium but in others the shift seems chiefly a mechanism for preventing large fluctuations in serum bicarbonate. Attention to the possibility of variation in the amount of intracellular sodium should clear up certain problems in which balances of

sodium do not explain the changes in serum electrolyte. In studies of this kind balances of nitrogen, chloride, sodium and potassium must be determined along with serum concentrations.

If further study shows that loss of intracellular sodium is a frequent accompaniment of acidosis, this factor will have to be taken into account in calculating the dose of sodium bicarbonate which is necessary to restore serum bicarbonate. Thus treatment of acidosis may require (1) enough sodium bicarbonate to make up the deficit in bicarbonate concentration in the dehydrated extracellular fluids, (2) enough sodium bicarbonate together with appropriate amounts of sodium chloride to restore the volume of extracelluar fluids, and (3) enough sodium bicarbonate to replace intracellular sodium. The first factor equals the deficit in serum concentration of bicarbonate times the dehydrated extracellular water, the latter usually being less than normal in a dehydrated patient. The expansion of extracellular water can be appropriately taken care of by balanced solutions containing sodium bicarbonate (or equivalent) as well as sodium chloride such as artificial interstitial salt solution or Hartmann's lactate-Ringers. The third factor is about 0.4 weight times 10 if all intracellular sodium is lost and the intracellular loss is confined to muscle. Thinking in these terms should place electrolyte therapy on a more rational basis and lead to a better understanding of disturbances in water and electrolyte balance.

At present the significance of marked loss of intracellular potassium and phosphorus such as is shown in Case 9 is not known but presumably it represents a serious change in the composition of cytoplasm. Guest and Rapoport[25] have described loss of phosphorus in acidosis and ascribe it to changes in the type of intracellular phosphorus compounds. Harrison and Harrison[26] have pointed out that renal loss of phophorus may be expected in acidosis owing to failure of tubular reabsorption of phosphorus. In the calculation of the expected balance of potassium and phosphorus the correction for the balance of nitrogen is probably too large since a rise in the concentration of nonprotein nitrogen was not taken into account. If the rise of nonprotein nitrogen was as high as 1 Gm. per liter of body water, the correction in a baby weighing 2 kg. might be about 4 mM too high for potassium and 3, for phosphorus. Only in Case 9 is the calculated correction likely to be in error by this much. Lack of data on the nonprotein nitrogen, therefore, is not likely to alter the general trends shown in Tables VIII and IX.

SUMMARY

Feeding with protein milk powder with or without added carbohydrate produces acidosis in premature infants. The acidosis is characterized by low pH, low bicarbonate, and usually high chloride in the serum. The babies become pale, listless, lose their appetite, and sometimes show Kussmaul breathing; neither loose stools nor ketosis develop.

Balance studies show that the acidosis is due to excessive retention of chloride in relation to sodium. The relative excess of chloride is equivalent to about one-third of that normally present in extracellular fluids. In this process, extracellular water increases, intracellular water decreases and weight is lost. Intracellular sodium is transferred to extracellular fluids in amounts equivalent to about all the sodium which is normally in the intracellular phase of muscle. In one case a deficit of phosphate and potassium developed but in the other cases the retentions of nitrogen, phosphorus, potassium, and calcium were essentially normal.

The acidosis can be prevented by the addition of sodium bicarbonate to protein milk powder. Acidosis does not develop on HI-PRO, a food of similar organic but different electrolyte composition. In the manufacture of protein milk powder about 2 mM of calcium is added and 2 mM of sodium is lost per 100 calories and is sufficient to explain the development of acidosis.

It is pointed out that the poor renal function of premature infants explains their susceptibility to small changes in the intake of sodium and chloride. It is likely that this fact must be taken into account in other foods used for feeding premature and young infants.

The importance of transfer of intracellular sodium to extracellular fluids is discussed. The amount involved is equivalent to one-ninth of total extracellular sodium or a large part of extracellular sodium bicarbonate. This quantity probably plays an important rôle in other types of acidosis and must be considered in estimating the deficit of body sodium in acidosis.

PROTOCOLS

CASE 5.—The patient was a normal, premature boy born May 4, 1943, weighing 2,120 Gm. and measuring 45 cm. He was fed on cow's milk with 2 per cent fat and 10 per cent added carbohydrate except for three days of the metabolic study. His course was uneventful except for the metabolic study. He was discharged on the thirty-first day weighing 2,500 Gm.

The metabolic study was for three days on 270 c.c. of milk with 2 per cent fat and 10 per cent added carbohydrate (May 23, 24, 25). This was followed immmediately by three days (May 26, 27, 28) on protein milk powder, 50 Gm. in 270 c.c. of water. The weights were 2,160, 2,260, and 2,075 on May 23, 25, and 28, respectively. At the end of the feeding with protein milk powder, he looked sick, with sunken eyes, grey color, poor skin turgor, and moderate Kussmaul breathing. Recovery was rapid after an infusion of 60 c.c. of 10 per cent glucose containing 1 Gm. of $NaHCO_3$.

CASE 6.—The boy was born November 19 after an estimated gestation of eight months. No trouble was encountered at birth. The weight was 2,340 Gm. and the length, 43 cm. The baby was given cow's milk with 2 per cent fat and 10 per cent added carbohydrate starting on the second day and increasing gradually to 110 calories per kilogram by the tenth day of life. The food was changed to cow's milk plus 5 per cent dextrimaltose on the fourteenth day of life. This mixture was used during the days preceding the metabolic study. The metabolic period was for two days, December 8 and 9, and the formula was protein milk powder 70 Gm., water 330 c.c., six feedings of 50 c.c. The weights are given in the balance table. A few cubic centimeters of urine were probably mixed with the stools, but otherwise the collections were satisfactory. No serious disturbance was clinically evident at the end of the period. The baby was discharged December 15, weighing 2,520 Gm.

CASE 7.—The boy was born Dec. 31, 1943, after about seven months' gestation. The birth weight was 1,120 Gm. and the length 37 cm. The baby was given milk with 2 per cent fat and 10 per cent added dextrimaltose gradually increasing the intake to 100 calories per kilogram by the thirteenth day. On the fifteenth to nineteenth days, he had skin lesions about the buttocks that looked like impetigo. Cultures were negative for streptococci. He seemed to respond to oral riboflavin and sulfathiazole applied locally. With this exception, he did well being discharged on the eighty-sixth day weighing 2,410 Gm.

The metabolic study lasted three days starting Feb. 21, 1944, (age 53 days). Initial and final weights of the period were 2,085 and 2,080 Gm. The food was protein milk powder 50 Gm., 0.9 Gm. $NaHCO_3$ and 260 c.c. water, eight feedings of 30 c.c. Although the child acted somewhat listless and looked pale at the end of the metabolic study, no serious disturbance was evident clinically.

CASE 8.—The baby was a Negro boy born May 21, 1944. The apparent gestation was seven and one-half months and the birth weight, 2,315 Gm. He was fed milk with 2 per cent fat and 10 per cent added dextrimaltose gradually increasing the intake to 95 calories per kilogram by the tenth day. The metabolic period was for three days starting May 30 (age, 9 days). The caloric intake was the same as previously taken. The formula

was: HI-PRO 60 Gm., water 300 c.c., eight feedings of 30 c.c. The daily weights were 2,280, 2,255, 2,245, and 2,255 Gm. No symptoms developed during the study. On the original formula, he did well being discharged at 4 weeks weighing 2,640 Gm.

CASE 9.—The boy was born April 5, 1944. There are two older healthy siblings. Despite an anti-Rh titer at a dilution of 1 to 8 in the mother's blood, and Rh-positive blood in the father and this baby, no symptoms referable to erythroblastosis developed in this or the previous pregnancies.

The birth weight was 2,025 Gm. He was fed milk with 2 per cent fat and 10 per cent added carbohydrate, gradually increasing the intake to 100 calories per kilogram by the tenth day. On the twentieth day (April 24) the metabolic study was started. This consisted of two periods of three days each on feedings containing the same caloric intake as had been taken previously. The first formula was: protein milk powder, 40 Gm., dextrimaltose 35 Gm., water 340 c.c., six feedings of 50 c.c. The second formula was: protein milk powder 67 Gm., water 340 c.c., six feedings of 50 c.c. The successive daily weights were: 2,480, not recorded, 2,425, 2,350, 2,345, 2,355, and 2,350 Gm. During the study the baby became pale and looked sick. He took all feedings except that 15 c.c. of two feedings were refused on the last day. He showed no acidotic breathing at the end of the study. At this time he was given a clysis of 80 c.c. of interstitial salt solution and an evaporated milk formula with 10 per cent sucrose. The next day he was given another clysis with Hartmann's lactate Ringer's and a transfusion of blood. At this time he developed Kussmaul breathing and fever (38.2). Both the temperature and acidotic breathing continued through the next day until he was given 60 c.c. of one-sixth molar sodium lactate and 40 c.c. of 5 per cent glucose subcutaneously. Thereafter the baby did well being discharged on the thirty-fifth day weighing 2,630 Gm.

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SALICYLATE THERAPY IN RHEUMATIC FEVER IN CHILDREN

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IT HAS been generally believed that salicylate therapy in rheumatic fever is empirical and does not modify in any significant degree the progress of the disease. It is, on the other hand, agreed by clinicians that the favorable effects of salicylates upon the course of acute rheumatic polyarthritis is striking and often dramatic enough to give the impression that salicylates may have a specific therapeutic effect upon the rheumatic process. The course of rheumatic activity, however, is not always influenced by salicylate therapy beyond the effect upon the joint manifestations. To date no evidence has been presented to show that other manifestations such as chorea, carditis, rheumatic nodules, or other skin manifestations are favorably modified by salicylate therapy. In addition, there is no clear-cut evidence to show that the beneficial effect of salicylate therapy upon rheumatic joint manifestations bears any significant relationship to the extent of cardiac damage.

The observation of Coburn[1] that massive salicylate therapy may modify "the sterile inflammatory reaction which occurs during activity of the rheumatic process" and thus "inhibits the development of cardiac disease" has once again opened the question of the specificity of salicylates as a therapeutic agent in rheumatic disease. The thoughtful postulate that the salicyl radical in proper concentration in the blood serum of a rheumatic patient may upset or indeed prevent the antigen and antibody reaction in rheumatic disease is stimulating but based upon a premise not as yet clearly shown to be fully responsible for the pathologic process operative in rheumatic disease. This postulate, however, demands a fundamental approach to the study of salicylate therapy in rheumatic disease.

Coburn points out that in order to produce the desired beneficial effect, the salicylate level in the blood plasma of the rheumatic patient must be high (from 350 to 450 gammas per cubic centimeter); that the intravenous administration of sodium salicylate is required to obtain such concentration in the blood plasma; and that when this level is obtained, the inflammatory reaction of rheumatic fever "can be suppressed to a degree that the disease process is not detectable by clinical or laboratory examinations," and "that the prompt suppression of rheumatic inflammation may prevent the development of the stigmata of heart disease."[1]

In the present paper, observations are presented on the use of massive doses of sodium salicylate in a group of children having active rheumatic disease. An attempt is made to draw a comparison between the intravenous and oral routes of administration of salicylate in regard to blood plasma levels; effects upon the course of active rheumatic arthritis; and the possible untoward effects or indeed hazards of the intravenous route. A further attempt is made to evaluate the effect of salicylate therapy upon the course of rheumatic carditis as distinct from that of polyarthritis.

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PATIENTS STUDIED

Sixty-four boys and girls, from 6 to 14 years of age were observed during the course of an acute rheumatic episode. Some of these children came under observation within forty-eight hours following the onset of the acute episode; others were admitted several weeks following the onset of the rheumatic process. All of these children were institutionalized* for weeks and in many instances for months following cessation of all clinical and laboratory evidence of rheumatic activity.

Since the manifestations of acute rheumatic disease are bizarre and often equivocal and difficult to diagnose, two clear-cut types of rheumatic manifestation were selected for the purpose of this study. One group of children presented clinically and by laboratory examination the classical picture of rheumatic polyarthritis without detectable evidence of carditis. The second group had rheumatic carditis† not preceded by any other rheumatic manifestations such as polyarthritis or chorea.

METHOD OF THERAPY AND FOLLOW-UP

Our patients were studied carefully before therapy was begun. This study included in addition to a routine physical examination and laboratory examination, cardiac, roentgenology, electrocardiography, blood studies, and in most instances determinations of the antistreptolysin and antifibrinolysin titers. Where epistaxis was a presenting symptom, prothrombin time and bleeding and clotting studies were made. When all studies were completed therapy was instituted.

1. *Intravenous Salicylates.*—A 1 per cent solution of sodium salicylate in sterile saline was prepared daily as needed. The total dose of sodium salicylate was calculated for each child on the basis of 1 grain per pound of body weight and the equivalent amount of the 1 per cent solution was given intravenously by the drop method to be administered in a period of six hours. Thus, a child weighing 70 pounds received 700 c.c. of a 1 per cent solution of sodium salicylate in a period of six hours. This procedure was repeated daily for six days. After the sixth day period of intravenous therapy, sodium salicylate in dosage of 1½ grains per pound of body weight was continued by mouth for a total period of thirty days.

2. *Oral Salicylates.*—

(a) *Massive Doses:* Sodium salicylate and sodium bicarbonate in equivalent doses were given in powder or tablet form every four hours. The total daily dose was determined as that dose which raised the blood plasma level to 300 to 450 gammas per cubic centimeter. This was found to be about 1½ grains per pound of body weight. In a few instances a larger dose was required to raise the blood plasma level to the desired concentration. The oral administration of salicylates was continued for an average of thirty days. In some instances the high degree of rheumatic activity necessitated the use of this therapy for several weeks longer.

(b) *Small Doses:* Some children were given small doses of salicylates (less than 1 grain per pound of body weight). The salicylates were continued until the sedimentation rate had returned to normal.

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*The average stay of our rheumatic patients at the Kings County Hospital was about four weeks following the cessation of rheumatic activity. The stay at St. Francis Sanatorium is a minimum of six months following rheumatic activity.

†The criteria used for the diagnosis of rheumatic carditis were: tumultuous cardiac action, changing cardiac murmurs, significant electrocardiographic findings, a low haemic component which failed to improve with a normal well-balanced diet, failure to gain weight continuously and a low vital capacity.

3. *General Care.*—All children under observation received a wholesome, well-balanced diet without preponderant emphasis upon synthetic vitamins. Those children who manifested tendencies to epistaxis were given vitamins K and C in moderate doses. Cardiac therapy was limited only to cases showing incipient or frank heart failure. Local therapy to joints was not withheld where pain was severe; but no other analgesics were administered beyond salicylates for painful joints. Sedation for restlessness and insomnia was given freely.

4. *Follow-up Studies.*—Blood plasma salicylate levels were determined daily during the first six days of treatment and weekly thereafter. Sedimentation rates were read biweekly. Other studies were done as indicated to follow the course of rheumatic activity.

RESULTS

1. *Rheumatic Polyarthritis.*—

Group I. Children who received intravenous salicylates for rheumatic polyarthritis (Table I, Group I): Seven children were given salicylates intravenously during the course of rheumatic polyarthritis. The suppression of the arthritic manifestations was prompt following the institution of treatment. The temperature dropped within forty-eight hours. All other presening symptoms such as restlessness, fatigue, and anorexia subsided and the patient presented a distinct picture of well-being before the course of intravenous therapy was concluded. The sedimentation rate dropped to normal in an average of about four weeks for the entire group. In one case it returned to a normal level in eleven days and the slowest return to normal in another case was forty-nine days. Repeated blood plasma level determinations showed a fluctuation of from 300 to 450 gammas per cubic centimeter and this level was maintained until therapy was stopped.

Six of the seven children developed symptoms of salicylism not sufficiently annoying to necessitate interruption of therapy, but definite enough to be of some concern. All these patients complained of severe tinnitis, some had anorexia, and two children were disturbed frequently by repeated bouts of emesis. No hemorrhagic manifestations were encountered in this group and none developed signs and symptoms of acidosis.

Group II. Children who received massive oral doses of salicylates for rheumatic polyarthritis (Table I, Group II): Seven children were given sodium salicylate by mouth in massive doses (about 1½ grains per pound of body weight) at onset for an attack of rheumatic polyarthritis. The blood plasma salicylate in this group of children rose to the same level as in the intravenous group. The initial rise, however, was delayed for thirty-six to forty-eight hours after the onset of therapy.

In this group of children the suppression of the arthritic manifestations was prompt but not as dramatic as in the intravenous group of children. All symptoms, however, subsided rapidly and completely within several days of the beginning of the therapy. The drop in the sedimentation rate to normal was delayed for a significantly longer period than in the intravenous group. While one case showed a return to normal in twenty-one days, the rest of the cases presented an elevated sedimentation rate for more than seven weeks. In one instance the sedimentation rate did not return to normal for twenty-three weeks. However, recovery was complete and no progressive cardiac damage could be detected. None of these children complained of symptoms of salicylism, and no hemorrhagic manifestations were observed.

TABLE I. EFFECT OF SALICYLATES ON RHEUMATIC POLYARTHRITIS

GROUP I. INTRAVENOUS ROUTE						GROUP II. ORAL ROUTE					
NAME	SALICYL. LEVEL GAMMAS/C.C.	DURATION ELEVATED SED. RATE (DAYS)	SYMPTOMS OF SALICYLISM*		RECOVERED	NAME	SALICYL. LEVEL GAMMAS/C.C.	DURATION ELEVATED SED. RATE (DAYS)	SYMPTOMS OF SALICYLISM	RECOVERED
G. S.	350 to 400	11	T		Yes	I. B.	300 to 400	21	–	Yes
F. W.	400 to 500	16			Yes	S. Q.	300 to 350	44	–	Yes
V. V.	300 to 450	16	T		Yes	H. C.	350 to 400	49	–	Yes
J. M.	200 to 250	26	T	A	Yes	M. F.	350 to 400	49	–	Yes
A. S.	350 to 450	28	T	A V	Yes	J. P.	400 to 450	56	–	Yes
C. L.	350 to 400	42	T		Yes	A. L.	400 to 450	60	–	Yes
R. R.	300 to 500	49	T	A V	Yes	A. P.	300 to 400	161	–	Yes
Average	350 to 450	26.8	6 Patients		All	Average	350 to 400	63	None	All

*T, tinnitis; A, anorexia; V, vomiting.

2. *Rheumatic Carditis.—*

Group III. Children who received sodium salicylates intravenously for rheumatic carditis: Two children were admitted to Kings County Hospital with a severe form of rheumatic carditis. One of these presented the earliest symptoms of rheumatic activity seven days prior to admission and the other child thirty-five days prior to admission. Both children showed definite signs of acute carditis with symptoms of incipient left heart failure. In each case intravenous salicylate therapy was begun within forty-eight hours of admission.

Both children reacted poorly to this form of therapy. Although the initial reaction was a drop in temperature and an apparent clinical improvement, a hyperpneiac type of tachypnea developed on the third day of treatment. This striking tachypnea was out of all proportion to the signs of left heart failure and persisted during the entire course of salicylate therapy. Repeated urine examinations failed to disclose acetone and the blood carbon dioxide concentration was slightly on the alkaline side. Prolonged prothrombin time was controlled with moderate doses of vitamin K. All forms of therapy aimed at relieving the respiratory distress were unsuccessful. Both children died in heart failure, completely disoriented and with the symptom of respiratory distress predominating. Unfortunately, permission for autopsy was not granted in either case.

Group IV. Children with rheumatic carditis who received massive doses of sodium salicylate by mouth at the onset of the rheumatic episode (Table II, Group IV): Six children were given massive doses of sodium salicylate by mouth at the onset of an attack of acute rheumatic carditis. In these cases frequent plasma salicylate levels were determined and found to range between 350 to 450 gammas per cubic centimeter.

None of these children presented untoward salicylate symptoms. The sedimentation rate returned to normal within an average of nine weeks. All of these children showed complete recovery within two weeks after the sedimentation rate had returned to normal. There was no palpable evidence of any advance in cardiac damage.

Group V. Children with rheumatic carditis who received massive doses of sodium salicylate by mouth; treatment begun several weeks after onset of carditis (Table II, Group V): Six children came under observation with a history of rheumatic carditis of many weeks' duration. As far as could be

TABLE II. EFFECT OF SALICYLATES ON RHEUMATIC CARDITIS—MASSIVE DOSES

GROUP IV. TREATMENT AT ONSET				GROUP V. TREATMENT WEEKS AFTER ONSET				
NAME	DURATION ELEVATED SED. RATE (WEEKS)	SYMPTOMS OF SALICYLISM	RECOVERED	NAME	DURATION ELEVATED SED. RATE (WEEKS)	SYMPTOMS OF SALICYLISM	RECOVERED	DURATION OF ACTIVITY BEFORE TREATMENT (WEEKS)
E. K.	6	–	Yes	A. G.	8	–	No	43
E. G.	6	–	Yes	M. E.	9	–	Yes	6
R. D.	7	–	Yes	A. M.	14	–	Yes	6
E. L.	7	–	Yes	A. D.	34	–	Yes	28
A. T.	10	–	Yes	M. F.	36	–	Yes	36
H. P.	20	–	Yes	G. W.	71	–	Yes	20
Average	9.3	None	All	Average	28.6	None	5 (83.3%)	23.1

determined, no consistent salicylate therapy had been administered during the period of rheumatic activity preceding admission to the sanatorium. These children were acutely ill and presented unequivocal evidence of carditis. The average duration of rheumatic activity prior to the institution of massive salicylates was twenty-three weeks. Blood plasma salicylate levels were not determined in this group of children. The oral dose of sodium salicylate given, however, was calculated in the same manner as in Group IV in whom the level was found to be 350 to 450 gammas per cubic centimeter. Salicylates were continued until the sedimentation rate returned to normal.

Five of the six children recovered completely at the end of the course of treatment. The return of the sedimentation rate to a normal level, however, was delayed for a much longer period than in the group of children who received massive salicylate therapy at the onset of rheumatic activity. The average period during which the sedimentation rate remained elevated in this group was 28.6 weeks. One of the children failed to recover for many weeks after the sedimentation rate had returned to normal. It should be noted, however, that in this case there was a history of active rheumatic disease for nearly one year prior to the institution of the massive salicylate therapy. One child with rheumatic carditis receiving massive doses of salicylate was omitted from this group as the therapy could not be continued beyond a few days when alarming signs of tachypnea developed. This patient continued to have active carditis with definite evidence of heart failure.

Group VI. Children with rheumatic carditis who received the usual small doses of sodium salicylate at the onset of rheumatic carditis (Table III, Group VI): Five children who came under observation at the onset of a recurrence of rheumatic carditis were given the usual small doses of salicylate by mouth. This form of therapy was continued until the sedimentation rate had returned to a normal level and remained at this level for three successive determinations made one week apart.

It was noted that in most of the children in this group the sedimentation rate returned to normal promptly; an average period of 10.9 weeks from the beginning of therapy. This compares well with the group of children receiving massive doses of salicylate at the onset of rheumatic carditis. However, four of the five children treated continued to present evidence of active carditis for many weeks after the sedimentation rate had returned to normal level; a tumultuous cardiac rhythm, cardiographic deviation from normal, failure to gain weight, and a low vital capacity. In other words, rheumatic activity continued after suppression of the sedimentation rate was accomplished. All of

TABLE III. EFFECTS OF SALICYLATES ON RHEUMATIC CARDITIS—SMALL DOSES

GROUP VI. TREATMENT AT ONSET				GROUP VII. TREATMENT WEEKS AFTER ONSET				
NAME	DURATION ELEVATED SED. RATE (WEEKS)	SYMPTOMS OF SALICYLISM	RECOVERED	NAME	DURATION ELEVATED SED. RATE (WEEKS)	SYMPTOMS OF SALICYLISM	RECOVERED	DURATION OF ACTIVITY BEFORE TREATMENT (WEEKS)
J. B.	4	–	No	B. P.	7	–	Yes	2
M. L. D.	4	–	Yes	A. M.	8	–	No	13
E. McA.	5	–	No	M. V.	23	–	No	24
B. W.	10	–	No	H. C.	24	–	Yes	19
W. M.	36	–	No	L. C.	27	–	No	12
				G. G.	28	–	No	10
				F. D.	28	–	No	16
				D. G.	31	–	No	53
				M. V.	45	–	No	25
				D. C.	59	–	No	43
Average	10.9	None	1 (20%)	Average	28.0		2 (20%)	20.7

these children showed obvious progression of cardiac damage at the end of the period of obervation.

Group VII. Children with rheumatic carditis who received the usual small doses of sodium salicylate; treatment begun weeks after the onset of the rheumatic episode (Table III, Group VII): The children were observed during an attack of rheumatic carditis. The treatment consisted of bed rest, a wholesome diet, and the usual nursing care. No medication except sedation when indicated was administered. These children were observed for several weeks before salicylate therapy was instituted. At the end of this period of observation, small doses of sodium salicylate were administered and continued in most instances until the sedimentation rate returned to normal.

Only two of the ten children recovered completely at the end of the period of salicylate administration. The remaining eight children continued to show evidence of carditis for weeks and months following the return of the sedimentation rate to a normal level. Furthermore, the suppression of the elevated sedimentation rate was slow. For the entire group the average period during which the sedimentation rate remained elevated was twenty-eight weeks. This is comparable to Group V who received massive doses of salicylates weeks after the onset of rheumatic activity.

Group VIII. Children with rheumatic carditis who did not receive any salicylates during the entire period of rheumatic activity, (Table IV, Group VIII): A group of twenty-one children from 6 to 14 years of age were treated at the sanatorium during an attack of rheumatic carditis by complete bed rest and the usual nursing care and symptomatic treatment, withholding all forms of salicylate treatment. This group did not differ in any significant respect from any of the other groups we have noted. The nursing and medical care were precisely the same in both groups with the sole exception of the administration of salicylates.

The duration of rheumatic active carditis differed from case to case. The duration of the period during which the sedimentation rate remained elevated ranged from 13 to 117 weeks. Five children failed to show any evidence of rheumatic activity after the sedimentation rate had returned to normal and sixteen children presented obvious evidence of carditis for weeks after the

TABLE IV. RHEUMATIC CARDITIS TREATED WITHOUT SALICYLATES

NAME	*Group VIII* DURATION OF ELEVATED SED. RATE (WEEKS)	RECOVERED
M. G.	10	No
B. P.	12	No
M. H.	12	No
V. M.	13	No
S. Q.	14	Yes
R. R.	16	No
M. P.	16	No
M. O'C.	16	No
G. R.	18	Yes
L. A.	18	No
E. V.	18	Yes
M. DeP.	19	No
M. P.	20	Yes
D. P.	21	No
A. M.	23	No
E. D.	24	No
L. M.	33	Yes
V. M.	36	No
M. H.	38	No
R. S.	71	No
L. M.	117	No
Average	26.8	5 (23.8%)

sedimentation rate returned to a normal level. This evidence consisted of easy fatigability, a tumultuous cardiac rhythm, changes in cardiac murmurs, a low vital capacity, and frequent significant changes in the cardiogram. The sedimentation rate remained elevated for an average of 26.8 weeks for the entire group; for the group of five children who recovered after the sedimentation rate returned to normal, 23.8 weeks; and for the group who continued to demonstrate unequivocal signs of rheumatic activity after the sedimentation rate returned to normal, 29.7 weeks.*

Thus, the sedimentation rate remained elevated in this group as long as in the group of children who were treated late in the course of the disease with either small or massive doses of salicylate. The percentage incidence of recoveries, however, was significantly smaller in this group than in the group treated with massive salicylates.

CONCLUSIONS

Although the number of children observed in this study is small, the findings seem to be significant enough to warrant the following conclusions:

1. Rheumatic polyarthritis responds promptly and effectively to large doses of salicylates. This result can be attained by both oral and intravenous use of salicylates (Fig. 1). The intravenous route in our series of cases did not seem to offer significant advantages over the oral route provided the same plasma salicylate level is reached. No difficulty was encountered in reaching the desired plasma level with oral salicylate administration. The technical difficulties and the annoying symptoms ever present in the intravenous method of therapy in our experience outweigh the possible benefits derived from this method of shortening slightly the period during which rheumatic activity exists. Massive doses of salicylates in this group of cases did not present any thrombopenic disturbances and failed to show any detectable evidence of acidosis.

*The difference between 29.7 and 23.8 cannot be considered significant as the larger number is markedly enhanced by the presence of one instance in this group having a rapid sedimentation rate for 117 weeks. When this single case was omitted, the average is brought down to 19.1 weeks.

2. Massive doses of salicylates used in rheumatic carditis in children seem to produce equally prompt and effective results (Fig. 1). The sedimentation rate returns to normal as promptly as in the polyarthritic group provided the therapy is instituted at the onset of rheumatic activity. (Fig. 2.) When

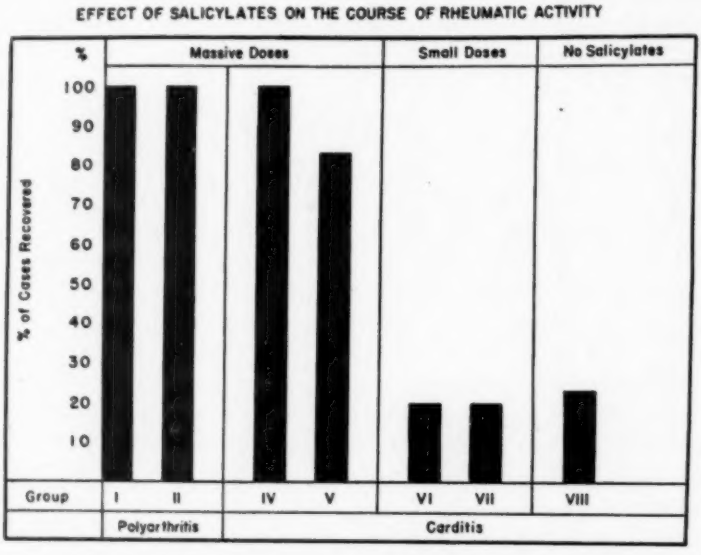

Fig. 1.—Percentage of patients who showed complete subsidence of all clinical evidence of rheumatic activity at the end of salicylate therapy.

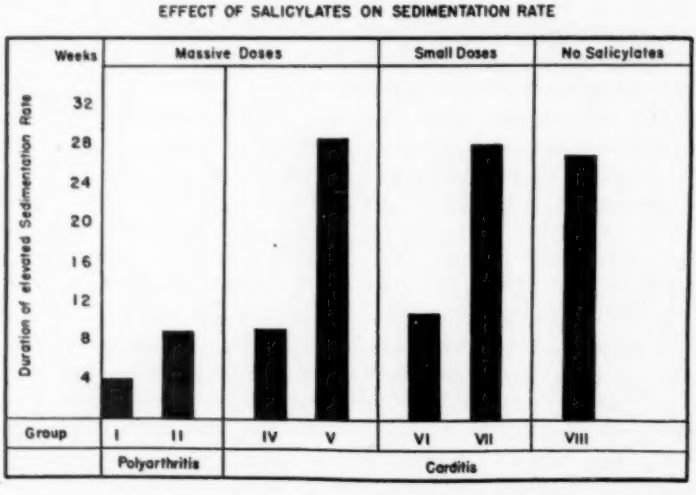

Fig. 2.—The average duration of the elevated sedimentation rate following salicylate therapy.

therapy is postponed, the subsidence of the rheumatic process is delayed for many weeks. All other signs of carditis, however, subsided at the same time as the sedimentation rate returned to normal. Intravenous therapy in this group may be hazardous.

3. Small doses of salicylates do not seem to affect the course of rheumatic carditis. The carditis seems to follow the same course whether insufficient

doses of salicylates are given or salicylate therapy is completely withheld (Fig. 1). The duration of the active process as measured by the presence of an elevated sedimentation rate is much longer than in the group receiving massive doses of salicylates. (Fig. 2.) Furthermore, when salicylates are withheld or given in small doses, the rheumatic process shows evidence of activity for a long period following the return of the sedimentation rate to the normal level.

COMMENT

The evasive character of mild rheumatic activity presents difficult problems in diagnosis. The use of a laboratory test such as the sedimentation rate as an index of rheumatic activity, falls notoriously short in making a diagnosis of mild, smouldering, rheumatic infection. Furthermore, minimal cardiac damage resulting from an acute rheumatic episode has often escaped the careful scrutiny of the most experienced clinician. In many instances years of follow-up are necessary to demonstrate such cardiac damage.

The evaluation of a therapeutic agent for rheumatic disease is thus fraught with many difficulties and pitfalls. The suppression of the sedimentation rate does not always signify a cessation of the rheumatic process. The subsidence of all clinical and laboratory evidence of rheumatic disease without detectable change in the cardiac status does not always forstall the advent of significant heart disease years later without obvious recurrence of rheumatic active disease.

On the other hand, the significant therapeutic results obtained from the use of large doses of salicylates seem to point the way to a new approach to salicylate therapy. While it cannot be definitely stated that massive salicylate therapy unequivocally suppresses the rheumatic process and prevents the stigmata of heart disease, it is clear that this form of treatment makes the patient symptom-free. Does this form of therapy suppress the symptoms and simply place the smouldering process under the clinical horizon or does it indeed break the chain of processes operative in rheumatic activity? Long follow-up studies of patients receiving this form of therapy might complete the story.

Furthermore, the introduction of a therapeutic agent must be ever concerned with the possible toxic effects of the drug. It has been pointed out that salicylate poisoning may produce serious manifestations.[2] The question has been raised whether or not the hemorrhagic tendency occasionally present in rheumatic fever may be an effect of salicylate therapy.[3] It has definitely been shown that salicylates in moderate doses consistently produce hypoprothrombinemia and hypocoagulability of the blood.[4, 5]

In our experience massive salicylate therapy may occasionally present definite hazards. This seems to be particularly true in intravenous salicylate therapy in rheumatic carditis. This form of therapy, therefore, should for the present be reserved for use by the most experienced investigators. More data must be presented to show the effect of a rapid rise of plasma salicylate level upon liver metabolism, its possible injurious effects, and the methods for neutralizing these effects, before the method is proposed for use generally.

SUMMARY

1. Observations on the effect of massive salicylate therapy in rheumatic polyarthritis and carditis are presented.

2. Our observations suggest that large doses of salicylates sufficient to raise the plasma salicylate level to from 350 to 450 gammas per cubic centimeter

produce a prompt and effective subsidence of all clinical and laboratory evidence of rheumatic activity in children having rheumatic polyarthritis. The oral route of administration is as effective as the intravenous.

3. Our experience further suggests that massive doses of salicylates in acute rheumatic carditis are equally effective in promptly suppressing all clinical and laboratory evidence of rheumatic activity. The intravenous route of administration seems to be hazardous.

4. The usual small doses of salicylates have no therapeutic value in rheumatic carditis in children.

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POLIOMYELITIS AND RECENT TONSILLECTOMY

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THE relationship of recent tonsillectomy to the occurrence of bulbar poliomyelitis has been studied by several investigators. Most of these reports confirm the original suggestion of Ayer[1] and Aycock and Luther[2] that a recent tonsillectomy predisposes the development of a bulbar or bulbospinal poliomyelitis within thirty days following the operation. These studies have been summarized by Aycock[3] who stated that acute poliomyelitis occurs more often among recently tonsillectomized children and that the increased incidence is due to the excess of bulbar cases which predominate over the spinal form in a ratio of five to one.

While considerable evidence supporting this relationship already exists, the occurrence of an epidemic of poliomyelitis in the state of Utah in 1943 presented an unusual opportunity to study this problem.

In 1943 the state of Utah experienced the most severe epidemic of poliomyelitis in its history and suffered more cases per capita population than any other state. Several features of this epidemic are of interest. The number of cases per month was as follows: January, 2; February, 2; March, 3; April, 5; May, 2; June, 3; July, 7; August, 43; September, 211; October, 62; November, 33; and December, 27. Due to the geographic location of the population, condensed primarily in the Salt Lake Valley, 69 per cent of the cases occurred in Salt Lake and Utah Counties. Ten of the twenty-nine counties in the state reported no cases. The only isolation unit for contagious diseases is located at the Salt Lake General Hospital; thus, only 136 of the 400 cases that occurred were hospitalized. This inadequacy necessitated the acceptance of only the patients who were reported by the local physician to have bulbar, or respiratory involvement to the exclusion of those who were spinal cases. This resulted in the admission of practically all of the clinically recognizable bulbar

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and respiratory cases. Thus, 31.6 per cent of the hospitalized cases were of the bulbar or bulbospinal type. The frequency with which a history of a recent tonsillectomy was encountered in these patients led to this study. Relatively few adults were affected with poliomyelitis, as 89 per cent of the cases occurred in individuals under 20 years of age, and 63 per cent in those under 11 years of age.

METHOD OF STUDY

A questionnaire was sent to 334 doctors in the state requesting the following information: (1) The number of tonsillectomies on children between 3 and 16 years of age done by them in July, August, and September of 1943. (2) The number of cases of poliomyelitis following recent tonsillectomy in these three months. (3) The age, sex, and name of the child. (4) The interval between operation and the onset of symptoms. (5) The doctor's name, if he wished, or (6) the county in which he practiced.

In addition to the information obtained by this questionnaire, all but two of the patients reported by the physicians were admitted to the Salt Lake General Hospital Contagious Disease Service.

RESULTS

The results of the study are tabulated in Tables I and II. Two hundred and forty of 334 doctors reported. Thirty-nine of these doctors, from whom statements were obtained subsequently, did not report for one of the following reasons: (1) They were in teaching or public health work. (2) There were no cases in their county. (3) They did no tonsillectomies. The reasons for failure to report in the remaining fifty-five doctors is not known. Thus 81 per cent, or 240, of 295 doctors who had reason to report returned the questionnaire.

The number of tonsillectomies done in the period was 1,411 in July, 2,111 in August, and 677 in September. In this same period there were seventeen of these tonsillectomized children who developed poliomyelitis within thirty days of the operation. All of these cases were of the bulbar or bulbospinal type.

TABLE I

Number of tonsillectomies done in July, August, and September on children between 3 and 16 years of age and number of these children who developed poliomyelitis within thirty days following operation.

	JULY	AUGUST	SEPTEMBER	TOTAL
Tonsillectomies done	1,411	2,111	677	4,199
Bulbar or bulbospinal cases in 3 to 16 yr. age group preceded by tonsillectomy and adenoidectomy	1	3	13	17
Mean interval between operation and onset (days)	21	14.3	15.4	15.9

TABLE II

Per cent incidence of poliomyelitis and bulbar poliomyelitis in general child population and tonsillectomized child population.

	POPULATION	POLIOMYELITIS (CASES)	PER CENT INCIDENCE POLIOMYELITIS	POLIOMYELITIS (BULBAR CASES)	PER CENT INCIDENCE BULBAR CASES
General	156,000	232	0.152	39	.025
Tonsillectomized	4,199	17	0.404	17	.404

During this period of three months 261 cases of poliomyelitis occurred in the general population. Of these, 232 were in children between the ages of 3 and 16. Thus, the incidence of poliomyelitis in the tonsillectomized group was 0.404 per cent or 2.62 times greater than the 0.152 per cent incidence of poliomyelitis in the child population of the same age.*

The total number of bulbar or bulbospinal cases occurring in this age group during these three months was thirty-nine. Thus, seventeen, or 46 per cent, of the bulbar cases were preceded by a recent tonsillectomy.

In addition, when the per cent of bulbar cases in the general child population is compared with the per cent of bulbar cases in the tonsillectomized group it is found that during this epidemic the possibility of the tonsillectomized child contracting bulbar poliomyelitis was sixteen times greater than the child of the general population.

While it is not possible to compare accurately figures concerning the incidence of bulbar and bulbospinal poliomyelitis occurring subsequently to July, August, and September, as no questionnaires concerning this period were sent out, it is interesting to note that out of 105 cases of all ages which occurred in the last three months of the year there were only six cases, or 5.7 per cent, of bulbar or bulbospinal type. While in the preceding three months (July, August, and September) out of 261 cases of all ages there were 43 cases of the bulbar or bulbospinal type, or 16.4 per cent. The exact reasons for this decline are not known although the reduction in the number of tonsillectomies done may have contributed greatly. In Table I it will be noted that the number of tonsillectomies done fell from 1,411 in July to 677 in September. The number done in October was undoubtedly much less for several reasons. Many doctors ceased doing tonsillectomies as the epidemic became more intense; the newspapers published the relationship of tonsillectomy to poliomyelitis; public apprehension led to delay of school opening and the closing of public swimming places and confinement of children to their homes. Inasmuch as recent tonsillectomy appeared to almost double the incidence of bulbar cases in July, August, and September, the marked supposed decrease in number of operations in the last three months of the year would appear to explain a great part of the decline in bulbar cases from 16.4 per cent to 5.7 per cent in these two periods.

SUMMARY

During three months of the ascending part of an epidemic of poliomyelitis in Utah in 1943, 43 per cent of the bulbar and bulbospinal cases were preceded by a tonsillectomy within thirty days of the onset. The incidence of poliomyelitis in recently tonsillectomized children was found to be 2.6 times greater than in the general child population. The incidence of the bulbar and bulbospinal type of poliomyelitis was found to be sixteen times greater in recently tonsillectomized children than in the general child population.

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*There were approximately 11,500 to 12,000 children in each year age group in the state of Utah in 1940. Recent increase in population during the war would undoubtedly make this figure larger.

A QUANTITATIVE STUDY OF SALIVA GLUCOSE

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PRELIMINARY to an investigation of the effect of adding a ration of candy to the daily diets of young children, the saliva and blood sugar values were concomitantly determined for each of fifteen boys and the same number of girls. They were normal infants between the ages of 15 and 42 months, random samples under observation at St. Vincent's Infant and Maternity Hospital.

The Exton-Rose two-dose technique[1] for glucose tolerance was adopted for the study. The first determinations were made before breakfast, after a twelve-hour fasting period. An Evelyn photoelectric colorimeter was used for assaying the sugar and the results are shown in Table I. Immediately following the collection and titration of fasting blood and saliva (First Test) 12½ Gm. of glucose in water were administered by mouth. After a thirty-minute interval, second blood and saliva samples were collected and analyzed for sugar content (Second Test). At the same time, 12½ Gm. of glucose were again administered, and thirty minutes later blood and saliva were collected for the Third Test, completing the Exton-Rose procedure. Fifteen minutes later a fourth saliva sample was collected (Fourth Test) and titration repeated. All of the concomitant assays, as well as the final saliva sugar values, are tabulated for comparison in Table I.

The blood was obtained from the external jugular, and the saliva collected by suction or by voluntary spitting, care being taken to avoid either mechanical or psychological stimulation of its flow. In four instances we were unable to obtain saliva, and in one instance unable to obtain blood for analysis. A modification of the micromethod of Folin[2] and Folin-Malmros[3] described by those authors for a quantitative estimation of blood sugar was used for saliva sugar determinations. Only 0.2 c.c. of saliva was required with this technique, details of which have been published by Kortuem.[4]

An analysis of Table I shows fasting (first test) sugar values in the saliva to have ranged between 3 and 27 mg. per 100 c.c., an average of 10 mg. per cent for the thirty cases. At the second test, thirty minutes after the ingestion of 12½ Gm. of glucose, the saliva sugar assayed between 6 and 124 mg. per 100 c.c., an average of 35 mg. per cent. In the third test, thirty minutes after the second dose of glucose, saliva sugar values of between 6 and 175 mg. per 100 c.c. were obtained, an average of 51 mg. per cent. A fourth test of saliva alone, collected fifteen minutes later, showed a sugar level of between 6 and 65 mg. per 100 c.c., an average of 21 mg. per cent.

The fasting blood sugar (Table I) ranged between 70 and 130, with a mean value of 94. At the second test, made thirty minutes after the first ingestion of glucose, the range of blood sugar was between 92 and 161, an average of 125. During the third test, thirty minutes after the second dose of glucose, the range was between 102 and 183, an average of 132.

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†Deceased.

From the Laboratory of St. Vincent's Infant and Maternity Hospital.
Candy was supplied and this research aided by a grant from Mars Incorporated.

TABLE I. BLOOD AND SALIVA GLUCOSE IN MILLIGRAMS PER 100 C.C.

CASE	FIRST TEST FASTING		SECOND TEST (30 MINUTES AFTER FIRST DOSE 12½ GM. GLUCOSE)		THIRD TEST (30 MINUTES AFTER SECOND DOSE 12½ GM. GLUCOSE)		FOURTH TEST (15 MINUTES AFTER THIRD TEST)
	BLOOD	SALIVA	BLOOD	SALIVA	BLOOD	SALIVA	SALIVA
1	110.0	7.0	142.4	63.0	160.5	175.5	52.5
2	117.0	27.0	113.5	124.5	127.4	94.5	30.0
3	92.0	7.0	132.0	19.0	178.0	21.5	22.5
4	100.0	6.0	136.5	108.0	126.0	19.5	8.0
5	104.6	7.0	123.0	----	137.5	103.0	65.0
6	102.7	8.0	127.5	31.0	133.0	63.7	26.3
7	130.0	9.0	157.0	28.0	136.5	22.0	11.5
8	85.0	6.3	140.0	18.5	----	19.0	7.0
9	84.0	7.2	107.0	83.0	119.3	56.5	18.0
10	88.0	17.6	161.5	42.0	118.0	166.5	---
11	90.0	20.5	160.5	46.0	137.5	53.5	23.0
12	72.0	8.0	138.5	16.0	162.0	----	54.0
13	92.0	11.5	96.5	21.0	129.0	39.5	25.0
14	92.0	10.0	115.0	26.0	116.5	105.0	---
15	122.0	8.5	137.0	30.0	126.0	79.0	17.5
16	91.5	18.0	105.0	61.0	116.5	60.0	21.0
17	102.0	9.0	154.0	12.0	170.0	9.5	10.0
18	90.0	7.0	127.0	11.0	114.0	9.0	10.5
19	105.0	7.5	119.0	24.0	132.0	64.0	22.0
20	111.5	10.5	111.5	22.0	119.0	16.0	8.5
21	110.0	9.0	153.0	13.0	183.0	11.0	12.0
22	95.0	9.0	125.0	75.0	120.0	146.0	38.5
23	94.0	7.0	122.0	7.0	136.0	11.0	7.0
24	109.0	13.0	110.0	101.0	118.0	108.0	40.0
25	78.0	17.0	110.0	11.0	104.0	13.0	15.0
26	84.0	3.0	128.0	6.5	136.5	6.5	6.0
27	70.0	10.0	105.5	13.0	113.0	28.0	18.0
28	81.0	17.5	136.5	17.0	167.5	13.0	12.0
29	72.5	9.0	92.5	9.0	102.0	13.0	13.0
30	78.0	14.0	105.0	14.0	117.0	14.5	14.0
31	84.0	8.0	110.0	20.0	116.0	12.0	10.0
Mean Blood	94.7		125.7		132.4		
Mean Saliva		10.6		35.7		51.8	21.3

From Table I, it was deduced that there was no constant blood sugar/saliva sugar ratio, since of thirty-one children assayed under fasting conditions, blood sugar values above the average were found in thirteen, eleven of whom had saliva sugar of less than the average for the group at the first test. At this same test, eighteen were below the average in blood sugar, and eight of these were above the average in saliva sugar. At the second test, after glucose ingestion, fifteen were above the average in blood sugar, eleven of these below in saliva sugar; and fifteen were below in blood sugar, of whom five were above the average in saliva sugar values. In the third test, eleven were above the average in blood sugar, seven of whom were below in saliva sugar; and eighteen were below in blood sugar, nine of whom were above the average for this test in saliva sugar. It was noted that blood sugar above the average more frequently had saliva sugar below than above its average for a given test, and that in children with blood sugar lower than the average the saliva sugar was likewise more frequently below the average than above, that is, the blood sugar content was not the only factor determining saliva sugar values.

The mean curve and the extremes of distribution of saliva and blood sugar values for the four tests are shown for comparison in Fig. 1. The trend of the mean curves of both blood and saliva was parallel. However, in the second test, the percentage rise above fasting level in mean values of saliva sugar was much higher than the concomitant increase in blood sugar; 300 per cent in saliva sugar, compared to 30 in blood sugar, and the third test showed a

mean saliva rise above the preceding test of 50 per cent, compared to a blood sugar rise of 6 per cent. This was followed by a rapid fall in saliva sugar, from 51 to 21 mg. per 100 c.c. (60 per cent) fifteen minutes later. In addition, it was evident from the graph that the spread of sugar values following glucose ingestion was much wider for saliva than for blood.

SUMMARY AND DISCUSSION

The children observed in this study were under 42 months of age, had deciduous teeth, all free of caries, and lived in an institution under identical environmental conditions. This group was ideal for this basic study since saliva sugar values were obtained for children with good mouth hygiene, absence of caries, and the assay was not influenced by lactic acid forming, or other sugar reducing microorganisms lodged in carious pockets. It seemed reasonable to assume, therefore, that the assay of saliva sugar in this group was a fair sample of primary and basic values.

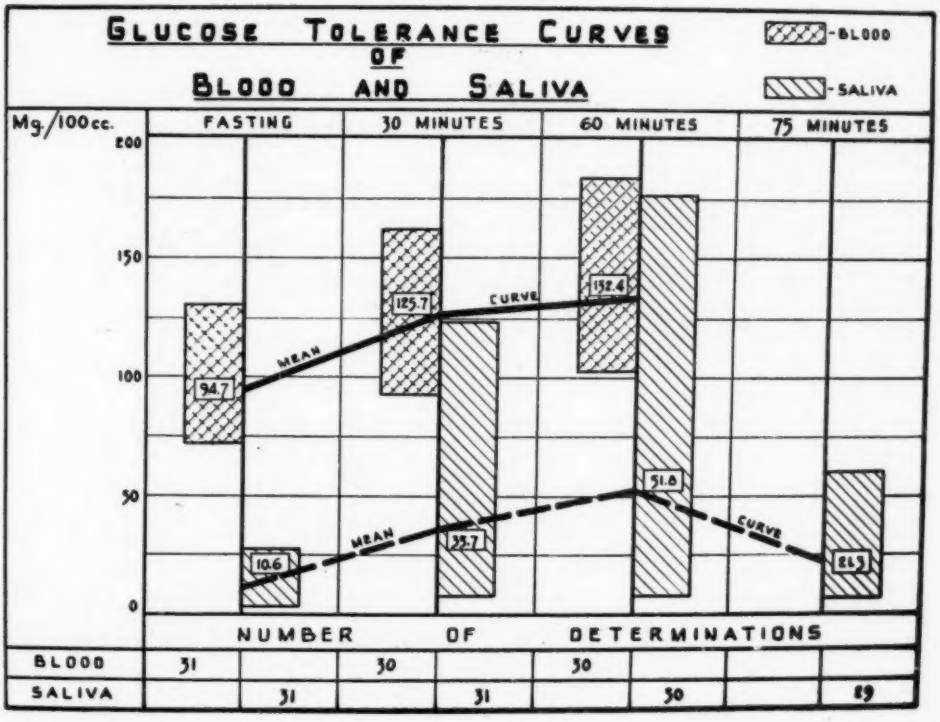

Fig. 1.

A wide irregular variability occurred in the per cent of saliva sugar when assays of individuals were compared under the same test conditions. In a few instances, irregularity was found in the same child in the four tests, but in general the trend of saliva sugar was upward following the ingestion of glucose and downward fifteen minutes later. This trend was confirmed by the arithmetical means in Table I, and graph line in Fig. 1. An equally interesting observation made from the table was the frequent and certainly unexpected divergence in concomitant blood-saliva sugar assays. The individuality of

results does not allow a ratio formula, although the mean curves of the two assays are similar. The contemplated continuation of the study with more cases may smooth out this angle. These irregular findings seem to us to be of more than academic interest in their possible relationship to the etiology and production of dental caries, since dental caries are reported by many authors[5] to occur equally irregularly among the individuals of families and racial groups. Blayney[6] suggests as one of the extrinsic factors in caries production "fermentable substance in saliva and tissue fluids." Glucose falls in this category, and it is possible that individual variations in the saliva content of this substance may be related to the individual variants in the incidence of caries. However, numerous investigators express the same opinion that Boyd[7] does in his conclusion that "sugar or starch has not been observed to favor caries, unless use of either materially diminished the amounts of ingested protective foods." The group studied at St. Vincent's Infant and Maternity Hospital was on what is usually considered an adequate diet, and in spite of the comparatively large amount of sugar in the saliva of some of these infants, none had caries. This seems to substantiate Boyd's observations.

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THE ALLERGIC CHILD IN CAMP

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AN IMPORTANT consideration in the treatment of any chronic disease, and this is especially true in childhood, is the attempt to prevent the patient from developing a sense of invalidism. The more a child can enjoy activities common to other children of his age, the happier and healthier he will be. Camps especially for diabetic children are highly successful and have contributed to our knowledge of diabetes in childhood. Camps especially for children suffering from allergic disease have not as yet been established, but with the advances which allergy is now making as a specialty, it is perhaps time to consider the desirability of organizing such camps. Meantime all pediatricians and allergists every summer are confronted with the problem of what to do about their young patients who wish to go to camp. So far as I can determine, this problem has not been dealt with previously in the literature and it is with the hope of stimulating interest in this field that this communication is made.

One of the primary considerations for such a camp is that there should be a resident physician in attendance. Previous experience in treating allergic children is highly desirable as a qualification for the camp physician but cannot be insisted upon at this time. Many camps, especially with the present shortage of physicians, employ a nurse for routine care of the campers and depend upon a physician in a neighboring town in case of necessity. This is not advisable in the camp to which an allergic child is to be sent. Not all allergic children, because of the nature and severity of their illness, should be permitted to go to camp, even if the parents are willing. Which child should or should not go is in every case an individual problem to be decided by consultation between the parents and the pediatric allergist or the parents, the allergist, and the pediatrician.

A child on a highly restricted diet should not be sent to camp because the difficulties inherent in carrying out such diets are accentuated by the increased appetite usually associated with camp life and activities. Even if the food allergy is associated with the ingestion of easily avoidable foods such as nuts or berries, the responsibility for avoiding these cannot be assumed by the camp management. In the case of a very cooperative child, it is a reasonable risk; otherwise not.

Before going to camp, any child, and particularly the allergic child, should have a thorough physical examination by a pediatrician. Many parents resent having their children examined when the child feels well but most do not resent having a well child thoroughly examined once a year. It is highly advantageous for the pediatrician to educate the parents of his camp age children to utilize the camp examination as the child's yearly physical examination. An important part of this examination is a check on whether or not the child has the prophylactic injections he should have had and has had a

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negative Schick test and has had a tuberculin test. Possibly the most important of the prophylactic injections next to smallpox vaccination is that of tetanus toxoid. While there is no simple practical test to determine whether or not these injections have been effective in any individual case, experience indicates that the procedure is highly effective. Tetanus has been practically eliminated from our army in this war[1] by immunization of soldiers with toxoid and no better evidence could be given. There are also, to my knowledge, no contraindications to administering tetanus toxoid to children whether allergic or not. For the past six years all the children in my practice have been routinely immunized against tetanus by means of toxoid, and only three disagreeable reactions have occurred; one consisted of a mild generalized urticaria and the other two of marked local swelling and induration. All three reactions subsided uneventfully. In the case of highly allergic children a preliminary test dose of 0.10 c.c. of toxoid subcutaneously is sometimes administered and the reaction noted, but since the report of Long[1] indicating that reactions to toxoid in the Army are less than one in ten thousand even this precaution is commonly omitted. Following the Army procedure I use the fluid toxoid. If by some chance, the child has not been immunized against tetanus by means of toxoid before he goes to camp, he may at least be given the first dose and arrangements made with the camp physician to administer the succeeding doses. In event this is not done and an indication for the use of tetanus antitoxin arises, the camp physician should be instructed to use bovine tetanus antitoxin[2] instead of the usual horse serum antitoxin, and if this is not available, or if the child is beef or milk sensitive, a despeciated antitoxin.

The problem of inoculation against typhoid fever is the same for the allergic child as for the nonallergic child. This is not yet a routine procedure in pediatric practice although with the simple and effective method described by Tuft[3] and favored by Ratner,[4] it could very well be. When the camp requests typhoid prophylaxis, it should be done. It should also be done if there is any question about the water supply of the prospective camp, either for drinking purposes or for swimming. Typhoid prophylaxis should be carried out if the campers are commonly taken on long hikes through the countryside because of the uncertainty of the purity of the water for drinking and bathing under such circumstances.

The most common allergic condition of the child at the camping age is pollinosis. The parents should take advantage of the opportunity for sending the child away to camp by sending him to a camp in an area as free as possible from the pollen to which he is sensitive. The child's allergist should be in a position to advise the parents as to the locale of such camps. Since ragweed pollinosis is the most common form, it is unfortunate that the conventional end of the summer camping season, because school starts immediately afterwards, is Labor Day which in many places, particularly northeasten United States, is the time when the ragweed is at its maximum period of pollination and the child must return to the highly polluted atmosphere of his home city if he is to start school at the same time as the other children. If possible, arrangements should be made to keep the child in camp until the height of the ragweed pollen season has passed at his home. The schooling which the child will miss is more than compensated by the gain in health occasioned by escaping the ragweed pollen.

Even though the child may go to camp in a pollen-free area, he should continue his treatments with pollen while in camp. If he is symptom free

there, he need not be given weekly injections but may receive injections every two or three weeks as the allergist may advise. The last dose of pollen in camp should be administered a few days before camp closes and the child on returning home should report shortly to his pediatrician with a record of his treatments and experiences in camp from the camp physician. There are several reasons for treating the child with pollen even though he may be going to a pollen-free area. If this is done and something happens, such as an accident or illness, to keep the child at home, he will be protected as far as possible from the pollen at home; the perennial method, which is the method of choice of most allergists, may be continued; and last, the continuous treatment with pollen extract, as far as we know, is the only hope for an ultimate cure other than naturally "outgrowing" the condition.

When the child leaves for camp, rather than send the material for treatment and the directions for its use to the camp physician, it is much more practical to send this by mail to the camp director to turn over to the camp physician. It is the camp director who knows the children and their parents best and who, even more than the camp physician, is interested in the success of the camp, and I have found by experience that the best results are obtained by putting responsibility for the child's treatments directly up to him. If given to the child to take along, the material and directions may be forgotten or kept in too warm a place until leaving or arrival at camp. It should be made clear to the camp director that the camp physician should communicate directly with the allergist if there is any doubt concerning the directions or the effect of the injections on the child. With the directions for treatment to the camp physician, or a report to him if the child is not to receive any treatments while in camp, should be listed particularly the child's drug idiosyncrasies, if any, and any other allergens to which the child is clinically sensitive, as well as any special directions which should be followed in camp.

The child should take to camp an adequate supply of all the medication he commonly uses for the treatment of his allergic condition. These medications should be plainly labelled as to what they are and how they are to be administered. The child should also take with him to camp his own bedding, if special pillows, blankets or blanket covers, and mattresses or mattress covers are necessary. Unless he rooms by himself, it will also be necessary to lend similar equipment to his camp mate.

The problem of swimming is often troublesome. This is permissible in the child with respiratory allergy if it is well under control, but not diving or swimming under water in the case of nasal allergy unless under perfect control because of the danger of forcing water into the sinuses or Eustachian tubes with their edematous mucous membranes. If the mere coldness of the water produces an allergic rhinitis or an asthmatic attack, then the child should not swim.

Children with chronic atopic dermatitis (dry eczema) may also swim, the lesions being protected with vaseline or some other bland ointment. The effects of swimming must be judged in each instance by the camp physician and if not well tolerated, must be discontinued. Exposure to sunlight is usually well tolerated by eczematous children but occasionally the eczema may be made worse by this exposure. If this happens, then exposure to sunlight must be controlled so as to prevent its ill effects. In any event the customary mad rush to acquire a good coat of tan as soon as possible after arriving at camp must be avoided particularly by eczematous children, in whom the exposure

should be gradual, starting with a ten-minute dose and gradually working up to the exposure tolerated by the other children. If a tar ointment is being used, the skin is particularly sensitized to sunlight and either special care must be used or an ointment not containing tar should be substituted. The skin of eczematous children is also prone to be irritated by overheating and perspiration which are likely to produce itching crises so these campers must be observed accordingly.

In general, the allergic child should avoid animals in camp as well as at home. If a child is not sensitive to horse dander, he may learn to ride but all his contacts with horses should be out of doors; not in barns or indoor riding stables. He should also use one particular outfit for riding which should be kept separate from his other clothes and not worn at any other time. In crafts and hobbies taught in camp, he should avoid the preparing and mounting of animals with fur or feathers. It would be better to interest the child in mineralogy or geology or the study of fossils or fish. He should not go on overnight hikes where he might have to sleep on the ground or in a barn. He should be taught to recognize and avoid poison ivy and should he be sensitive to this, prophylactic measures should be instituted before he goes to camp. Abnormally severe reactions to insect stings may occur and if this happens, the nature of the insect should be determined so that specific prophylactic therapy may be given if necessary. Fortunately bees, wasps, and ants have a common antigen so that protection against one protects against the others.[5] The other common offenders, mosquitoes, fleas, and bedbugs, belong to different classes of insects.

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CONGENITAL DERMAL SINUS AS A SOURCE OF MENINGEAL INFECTION

Report of Two Cases, One Associated With Recurrent Meningitis

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Charleston, S. C.

IN 1934 Walker and Buey[1] reported seven cases of congenital dermal sinus situated in the midline of the back. From small dimples in the skin epithelial tubes extended through unfused spinal laminae to the meninges of the spinal cord and furnished pathways by which infection spread to these structures. All of the cases except one were associated with spina bifida occulta. We were unable to find any other examples of this congenital malformation recorded in literature except the following. O'Connell[2] in 1942 recorded a case of a 4-year-old girl with a congenital dermal sinus in the lumbar region which was associated with recurrent attacks of meningitis. When 8 months old she had meningitis, and again at the age of 18 months, when the infection was accompanied by paralysis of the left leg. At operation the dermal sinus was traced through a defect in the neural arch of the fourth lumbar vertebra and was found to communicate with a large abscess which was within the dura and lying among the roots of the cauda equina. Recovery followed drainage and excision of the sinus. Sacrococcygeal and pilonidal sinuses have occasionally been the source of meningeal infection.[3, 4] Buey[5] in *Brennemann's Practice of Pediatrics* mentions two congenital dermal sinuses in association with spina bifida occulta. These sinuses he removed prior to the development of any meningeal infection.

Since this lesion is uncommon and may be the route by which infection reaches the meninges, we feel that the following two cases should be described in detail. One illustrates the complications which may supervene and emphasizes the importance of recognizing the condition and treating it before infection develops; the other shows the uneventful course and good results following removal of a sinus not complicated by infection.

Case 1.—A composite account of the history of this child, as obtained from the Children's Hospital in Chattanooga and the Roper Hospital, Charleston, S. C., is as follows:

A white girl, aged 10 years, had been born with a skin defect in the lumbar area thought to be associated with spina bifida. There was no paralysis or abnormality other than a large scarified area over the lumbar region. She had been delivered normally, was breast fed for 11 months, had teeth and walked at 1 year, and talked at 14 months.

On admission to the Children's Hospital, Chattanooga, in September, 1939, she had had insomnia and headache for a week, fever and backache for a day, and very intense headache for a few hours, during which time she had vomited twice.

Examination showed photophobia, stiffness of the neck, exaggerated patellar reflexes, and Kernig's and Brudzinski's signs present. The spinal fluid was ground-glass in appearance, with 157 cells, which increased to 800 cells two days later. The blood leucocyte count was 20,000, and the urine showed a moderate number of pus cells. It was thought that a streptococcus was present in the smears made from the spinal fluid, but culture was negative. Inoculation of a guinea pig caused death of the pig in five days, but no organisms were isolated. A roentgenogram of the chest showed nothing except a bifid fourth rib.

The patient was given 5 c.c. of neoprontosil solution intramuscularly and sulfanilamide by mouth. Improvement was steady and after nineteen days the child was discharged from the hospital apparently completely recovered.

From the Departments of Pediatrics and Pathology of the Medical College of the State of South Carolina.

Four months later, in January 1941, she was readmitted to the Children's Hospital with a history practically identical with that of the first attack. Her temperature was 103.2° F. She showed opisthotonos with a few scattered râles in the lungs. Spinal fluid cell count was 5,489, and a pure culture of meningococcus was obtained. She was given 40,000 units of meningococcus antitoxin intravenously and was put on sulfanilamide by mouth. Later she had two blood transfusions. Within a week she was considerably improved, though fever persisted for two weeks. Spinal fluid cultures became negative and cells decreased to 110 after eighteen days. She was finally discharged in good condition.

Eight months later, in September, 1941, for the third time this patient developed the same train of symptoms and was admitted to Roper Hospital. Her temperature was 104° F. and the blood leucocyte count was 25,000 with 93 per cent polymorphonuclears. The spinal fluid continued over 10,000 cells per millimeter, 95 per cent of which were polymorphonuclears. A culture showed hemolyzing *Staph. aureus*, which appeared repeatedly in subsequent cultures, and in two cultures was accompanied by a nonhemolyzing *Staph. aureus*. Blood culture was sterile.

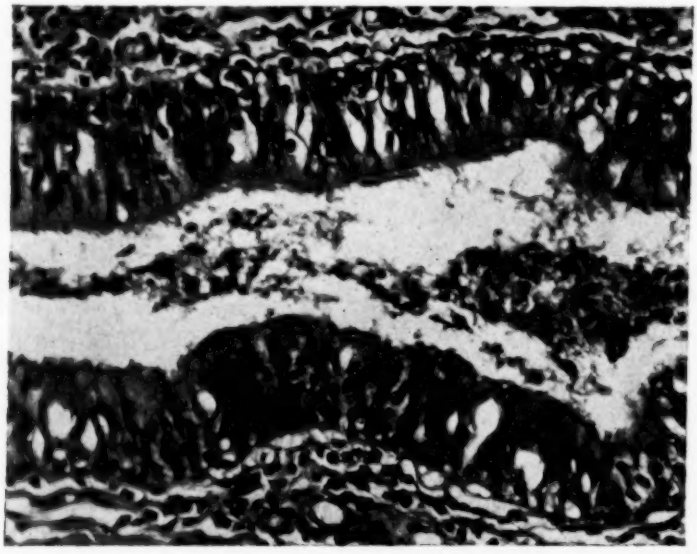

Fig. 1.—Sinus tract lined by ciliated pseudostratified columnar epithelium. Hematoxylin and eosin ×300.

The child was put on sulfapyridine by mouth and showed gradual improvement over a period of about two weeks. Sulfapyridine in the blood reached 7.05 mg. per 100 c.c. and in the spinal fluid was highest at 4.5 mg. There was a gradual decrease in the number of cells in the spinal fluid and a similar decrease in the proportion of polymorphonuclear leucocytes.

Fever lasted ten days. Stiffness of the neck and back persisted for some time after discharge from the hospital. Although sulfapyridine was continued and the patient improved, the spinal fluid seventeen days after admission still showed 256 cells with 20 per cent polymorphonuclears and culture still showed hemolyzing *Staph. aureus*. Three days later the culture was negative and only 147 cells were present.

In March, 1942, she was admitted for operation. A dermal sinus extended from the skin down into the spinal canal through a defect in the fifth lumbar vertebra. Culture from the sinus showed nonhemolyzing *Staph. aureus*. The patient went home five days after operation.

In August, 1942, she was readmitted with headache, weakness of legs, and inability to urinate. Her temperature was 103° F. and her spinal fluid showed 2,405 cells with 96 per cent polymorphonuclears. Two cultures of the fluid were negative. Sulfadiazine was given, sufficient to give a concentration of 6 mg. in the blood and 1.9 mg. in the spinal fluid.

There was gradual improvement, and the child was discharged eleven days after admission. She showed some difficulty with her left foot and both legs and had no bladder control.

On Oct. 12, 1942, she was readmitted for operation because of paralysis of her lower legs and loss of function of the cauda equina below the fourth lumbar area. At operation epidural granulation was found at the third lumbar area and a pocket of pus surrounded by friable membrane enveloped the nerve roots from the fourth lumbar to the first sacral and compressed the spinal cord. This abscess was evacuated and granulation tissue removed. Cultures revealed nonhemolyzing *Staph. aureus* and *albus*, and hemolyzing *Staph. albus*. Patient showed definite signs of recovery in dermatomes of the fifth lumbar, first and second sacral areas. Bladder function improved and she was discharged for orthopedic care of the residual paralysis of the feet.

Pathologic Examination: The elliptical excision of white skin and subcutaneous fat measured 4.2 cm. in length and 1.7 cm. in width. The center of the skin surface was puckered and wrinkled. Section through the center of the mass revealed a tubular structure within the center and perpendicular to the skin which measured 0.8 cm. in length.

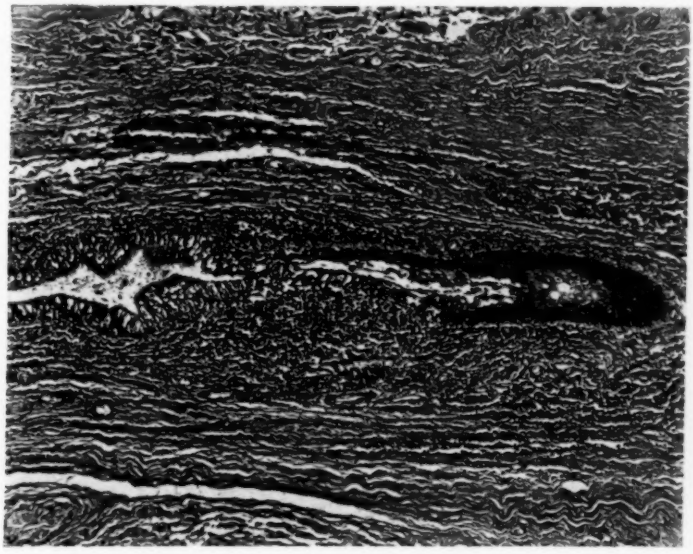

Fig. 2.—Low-power view of sinus to show merging of stratified squamous and ciliated columnar epithelium. Note heavy lymphocytic infiltration. Hematoxylin and eosin ×60.

Histologic study showed a sinus tract extending from the subcutaneous tissues toward the skin. The lining consisted of ciliated pseudostratified columnar epithelium (Fig. 1) having a well-defined basement membrane, but in the extremity toward the skin the lining was of stratified squamous epithelium (Fig. 2). About the sinus was heavy chronic inflammatory round cell infiltration. On all sides of the tract were zones of heavy fibrous tissue containing occasional nerve bundles and numerous calcospherites. Heavy scarring was present beneath the skin with occasional foci of lymphocytes and foreign body giant cells. Although the skin surface showed a definite depression no actual connection between the sinus and the skin surface could be demonstrated.

Case 2.*—A white girl, 16 months of age, was admitted to Roper Hospital on Oct. 10, 1942. She had always been in good health and had developed normally. At birth a small elevation was noted in the skin over the third lumbar vertebra and a small opening at the coccyx. There had been no urinary or fecal incontinence.

In the skin at the level of the third lumbar vertebra was an elliptical area of increased pigmentation measuring 6 cm. by 3 cm. In the center of this was a small dimple. There

*From the service of Dr. F. E. Kredel, who gave us permission to include this case.

was also an indentation 5 mm. in depth in the skin over the fifth sacral vertebra. The remainder of the physical examination was negative, except for slight eversion of the right foot with a mild degree of toe drop.

At operation a sinus tract was traced from the dimple in the skin down through a defect in the third lumbar vertebra to the dura. An elliptical portion of skin and the underlying sinus were excised in the lumbar region and the small dimple overlying the sacral vertebra was also removed.

Recovery was uneventful and the patient was discharged three days after the operation.

Pathologic Examination: The elliptical excision of white skin with a dimple in the center measured 5.5 cm. in length and 1.5 cm. in width. Extending beneath the subcutaneous fat was a cordlike structure measuring 1.5 cm. in length and 2 mm. in diameter. Its center was plugged with gray material.

Fig. 3.—Cross section of sinus showing wall composed of hyalinized fibrous tissue and degenerating epithelium mixed with nerve bundles. Hematoxylin and eosin ×55.

Microscopic study of sections cut perpendicularly to the skin showed a sinus tract beginning 3 mm. beneath the surface and extending downward in an undulating fashion with one lateral branching extension. The wall of the sinus was composed of dense collagenous fibrous tissue with an irregular lining of degenerating calcifying epithelium, apparently of squamous type (Fig. 3). Some nerve fibers were mingled with the tissues comprising the sinus wall and one nerve bundle was present in the lumen.

DISCUSSION

In the great majority of instances this developmental defect has been associated with spina bifida occulta. The probable manner in which these sinuses develop has been clearly described by Walker and Bucy.[1] They believe that in embryological development the cleavage between cutaneous epithelial ectoderm and neuroepithelial ectoderm is incomplete at the point where the sinus occurs and that the neural tube carried down an invagination of the skin. This forms an epithelial tube which may persist in childhood or even adult life.

The ciliated pseudostratified columnar epithelial lining of the sinus in the first case is of particular interest. None of the sinuses previously described has had a similar structure, although various teratomatous cysts of the central nervous system have possessed internal coats of this type. Kubie and Fulton[6]

reported two cases of teratomatous cysts of the spinal cord in which the lining was remarkably similar or even identical with that found here. The similarity of such linings to upper respiratory epithelium or that of the fetal gut is striking, but it is too difficult to see how entodermal implants could occur in this region of the body. Kubie and Fulton suggested that such cysts might be formed by the inclusion of a layer of ectodermal cells during the closure of the neural tube, a proposal which is very similar to the theory advanced by Walker and Bucy to explain the formation of the dermal sinuses. Kubie and Fulton also concluded that any type of fetal epithelium may under certain circumstances develop columnar epithelium possessing cilia. This we feel is probably true and offers an adequate explanation for the presence of this epithelium in the sinus, particularly since it merges with stratified squamous epithelium.

The development of a subdural abscess in the first case after the removal of the sinus was undoubtedly due to a persistent focus of infection in this region, which is not surprising when one considers the duration of the anomaly and the number of bouts of meningeal infection that preceded its removal. It does emphasize the necessity for early recognition and complete extirpation of the sinus.

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THE JOSEPH BRENNEMANN LIBRARY

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A LIBRARY bearing the distinguished name of Joseph Brennemann carries a proud responsibility. Himself a great teacher, Dr. Brennemann knew the value for students of ready access to the written word in pediatrics. The medical library in the Children's Memorial Hospital, where Joseph Brennemann was chief of staff for twenty years, symbolizes a tradition of study, of respect for the great names in pediatric literature, and of reliance on proved procedures of the past. Yet it symbolizes, too, a forward-looking approach to pediatric practice, an awareness of rapid and significant development of medical thought, and the principle that knowledge of the new must always temper belief in the old. A sentence from one of Joseph Brennemann's papers might well serve as a motto for the library he did so much to foster: "Medicine is coextensive with time itself, and he who no longer learns is medically moribund."

When Dr. Brennemann first came to the Children's Memorial Hospital in 1921 the medical library was in the hands of volunteers. As teaching courses developed and the postgraduate sessions began to prosper, the idea of making the library more effective in the educational program grew. In his annual report for 1934 Dr. Brennemann stressed the long-felt need of a wider development and better utilization of the library. The following year the staff decided to devote the proceeds of the postgraduate courses to the library, and arrangements were made for a full-time librarian, who should, as Dr. Brennemann stuplated, "know something about the inside of medical books as well as the outside."

Thus a start was made toward providing this "indispensable part of the equipment of the intern and the resident," to quote from Dr. Brennemann's report. The story of the library's steady growth is a testimony to Dr. Brennemann's beliefs. The library today, housed in newly designed, air-conditioned quarters, with ample, beautifully finished files, individual study desks, microfilm reading facilities—everything to make reading and study a pleasure—is a place all the hospital can point to with pride. All of this new physical equipment, and the name of the Joseph Brennemann Library, came to realization after Dr. Brennemann left the hospital at the end of 1940. On his last visit here, in June, 1944, Dr. Brennemann confessed that he was "sort of overwhelmed." We had come a long way in nine years.

Starting in 1935 with a library "unorganized, deficient in books and magazines . . . and poorly utilizable" (Dr. Brennemann's words again), the task of the librarian was twofold: first to organize and develop the material resources, and second—though first in importance—to speed the reference work of house doctors and visiting staff seeking help from medical literature.

Reorganization was a long-time job that was not to be allowed to interfere with day-to-day service. Rearrangement of books and journals on the shelves, replacement of missing numbers, revision of the catalog, all were promptly undertaken and continue to this day! But even the very beginnings were exciting. Residents began to come to the library and *find* things they were looking for instead of turning away discouraged or staying only to discuss base-

ball with each other. Long-lost books would stray *back* to the library, gifts came in, and the library in general began to look and to be "alive."

From the outset it was agreed that the policy of the library would be freedom from restrictions, with the greatest possible encouragement given to wide use of the library resources. Of his own personal books Joseph Brennemann used to say, "Anyone may borrow anything and keep it as long as he likes." We have tried to realize the same spirit of generosity in the library, only taking care to tie such library strings to borrowed material that it will come back eventually. Loan cards (in journals as well as books), identification marks, and occasional post card reminders have been sufficient except in rare instances to insure the safe return of loaned items. Library hours too are generous, even though the library has never had a staff of more than one. The library is open daily and on certain evenings, and the key is available to doctors at any other time.

The library's material growth was greatly accelerated by the addition of nearly all of Dr. Brennemann's private collection, including long runs of German periodicals and many valuable foreign language monographs. Gifts from the libraries of other pediatricians added to the store of basic texts and earlier reference works. Books selected by Dr. Abt from his library and given in memory of Joseph Brennemann are a late and highly prized acquisition.

Fig. 1.—Library bookplate.

A historical collection is in the making. Exhibit cases in the reading room are ready to receive additions to the few early nursing bottles now on display. Of particular interest to those who knew Dr. Brennemann is the exhibit of the specimens collected for his well-known study of curd. A memorial fund is being devoted to the purchase of early pediatric works, especially those pertaining to the surgery of childhood. The acquisition of other items of historical interest such as biographies, portraits, manuscripts is part of the library's program.

A rich background, this, for the current service the library offers. Upon this solid foundation have been built card-file bibliographies, covering a five-to-ten-year period with a fair degree of completeness for most subjects of recurrent interest to pediatricians. And for the many unusual conditions that come to a hospital such as this, similar bibliographies are steadily growing. An up-to-date reference file that strives to keep abreast of current publications is also at hand, so that the resident who comes in for something on the Rh factor, for instance, may easily learn the latest thought on the subject. Special files on drugs attempt at least to overtake the latest sulfanomide drug before a later

one appears. An index of infant foods has been started. In addition to these card files of references there are folders of articles in the form of reprints, clipped pages, and microfilms, arranged by subject for quick consultation or convenient lending.

To save the time of the busy doctor has always been a chief aim of the library. If there are indexes to be consulted this will usually be the task of the librarian, not the doctor. Residents—they are no longer medical school students—are encouraged to ask the librarian to look up and put out on reserve for them the references they need on any subject. Staff doctors telephone from their offices, alumni write back from out-of-town practices for references they want. Whether it is treatment for a particular case, technique for an unusual operation, method for a test, a work-up for a case presentation, or an exhaustive review of the literature for a publication—whatever the request, the Joseph Brennemann Library considers it a privilege to meet the need, either through its own resources or through contact with other libraries.

World War II has taken the library into new spheres of activity. With a large proportion of the hospital staff and alumni in military service, many of them have thought of the library most familiar to them when they have met unfamiliar problems in military medicine. The library develops its resources in broadening fields when it fills requests for material on chronic gastritis, neurocirculatory asthenia, or seasickness. The help the library supplies in cases of out-of-town requests is first, looking up the literature; second, sending reprints, clipped articles, journals, or microfilms, and occasionally books. The Joseph Brennemann Library has been able to send wanted medical literature to doctors in Alaska, Africa, the Aleutians, and wherever the APO number reaches.

Stimulating indeed to the accomplishment of the library aims were Dr. Brennemann's unstinted encouragement and his expressions of appreciation. In his last report for the hospital yearbook he said: "Only those who have been long and intimately associated with the work of the hospital can appreciate the intellectual stimulus that has come with the expansion and utilization of the medical library. . ." Speaking of the library as one of the indispensable units of the hospital, he concluded: "A backward step would be a loss that one would not like to contemplate." The Joseph Brennemann Library moves forward under the inspiration of a great name.

News and Notes

The following were certified by the *American Board of Pediatrics* at the examinations in Chicago, May 12 and 13, 1945:

Dr. Mary Daniel Ames, Children's Hospital, 5224 St. Antonine Street, Detroit 2, Mich.
Dr. Dale Ellis Beverly, 4306 South Parkway, Chicago, Ill.
Lieutenant Leonard L. Braun, Medical Corps, United States Naval Reserve, 5451 Cornell Avenue, Chicago, Ill.
Dr. Glidden Lantry Brooks, United States Public Health Service, 519 South Third Street, Muskogee, Okla.
Dr. John William Buckley, 2080 North Avenue, Bridgeport, Conn.
Dr. Virginia Murray Cobb, 310 Vally National Building, Tucson, Ariz.
Dr. Frank Stephen Cross, 426 West Ottawa Street, Lansing 15, Mich.
Dr. Joel Fleet, Louisiana State Medical School, New Orleans, La.
Lieutenant David Goldring, Oak Ridge Hospital, Oak Ridge, Tenn.
Dr. James Harrell Harris, 203½ North Washington Street, Marshall, Texas.
Lieutenant John Howard Laubscher, Army Service Forces Regional Hospital, Fort Benning, Ga.
Captain Selby V. Love, Oak Ridge Hospital, Oak Ridge, Tenn.
Dr. Sydney B. Mannel, 1575 Gilpin Street, Denver, Colo.
Dr. Eugenia Elizabeth Murphy, 1831 Wilson Boulevard, Arlington, Va.
Dr. Sidney Rosin, 6228 Wilshire Boulevard, Los Angeles 36, Cal.
Dr. Vincent J. Rounds, 1930 Truxtun Avenue, Bakersfield, Cal.
Dr. Edward Sager, 4802 Broadway, Chicago, Ill.
Dr. Richard Edward Wolf, 504 Carplin Place, Cincinnati 29, Ohio

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The American Board of Pediatrics announces that due to a new government ruling they have been unable to obtain hotel reservations in New York City for the Fall examinations. The examination has, therefore, been changed to Atlantic City, N. J., Hotel Claridge. An extra day has been added for the oral examination due to the large number of applicants.

The schedule is as follows:

Written examination—locally under a Monitor, Oct. 19, 1945
Oral examination—Atlantic City, N. J., Hotel Claridge, Dec. 7, 8, and 9, 1945

Recent information in regard to Latin-American Academy scholars is as follows:

Arrivals

Dr. Fernando Rene Leyva, of Cuba, is to begin under Dr. Irvine McQuarrie at the University of Minnesota July 1, 1945. He is now at Children's Hospital, Washington, D. C. (not on an Academy scholarship).

Dr. Manuel Antonio Jovel, of El Salvador, arrived at the University of Toronto, May 14, 1945, and will spend about three months working in the University Library while perfecting his English, before beginning his scholarship under Dr. Alan Brown.

Dr. Felipe Cacho de la Fuente, of Mexico, started May 1, 1945, to work in pathology at the Boston Children's Hospital under Dr. Sidney Farber and after six months will be in the service of Dr. Franc Ingraham, in surgery.

Dr. Beatriz Bienvenú, of Mexico, has been on an Academy scholarship under Dr. James Gamble at Harvard since March 12.

Dr. Rubén Lavalle, Dr. Lozoya's assistant in Mexico, spent two months brushing up on his English before beginning his scholarship at Western Reserve University on May 8, where he is working under Dr. John A. Toomey.

Departures This Summer

Dr. Ramón Sanz Muñoz, of Mexico, from Children's Memorial Hospital, Chicago, to Mexico, after a visit to various clinics.

Dr. Eduardo Cassorla Levy, of Chile, from University of Illinois, Chicago, to Chile, after visits to various clinics.

Transfer

Dr. Alfonso Cárdenas Murcia of Colombia, from University of Michigan to Children's Hospital, Boston (department of pathology), instead of clinic visits, for final four months of his scholarship June 4, 1945.

The deaths of the following have been reported to the JOURNAL:

Dr. Thomas E. Buckman, Jacksonville, Fla., on March 26.

Dr. Herman Schwarz, New York City, on May 18.

The Pediatrician and the War

Dr. Sidney R. Kaliski of San Antonio, Texas, and Dr. Tracy D. Peppers of Greeley, Colo., have received their discharges from the Army.

Dr. Jack Chesney of Knoxville, Tenn., is a Major in the Army Medical Corps.